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ΣΙΜΟΥ ΧΡΥΣΑΝΘΗΣ – Μεταπτυχιακή φοιτήτρια

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TITLE:

Mucinous Colorectal Adenocarcinoma: prognosis, diagnosis and treatment- A REVIEW

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1.Abstract: Mucinous colorectal adenocarcinoma (MAC) accounts for 1.6-25.4% of all colorectal cancers and is defined by the existence of extracellular mucin in more than 50% of the tumor volume. The prognosis of MAC compared to typical adenocarcinoma has been questioned in several studies. Typically, MACs are diagnosed in a more advanced stage, are less responsive to chemotherapy, and exhibit a higher number of involved lymph nodes and peritoneal metastases. Moreover, mucinous differentiation is associated with specific microscopic, molecular, and epigenetic features, such as a higher rate of microsatellite instability (MSI), CpG island methylation phenotype and BRAF mutation compared to non-mucinous colorectal cancers. Nevertheless, current clinical guidelines do not provide recommendations tailored to the management of this specific subtype of colorectal cancer. In this review, we explore the current literature in order to summarize the epidemiology and prognosis, the distinct clinicopathological traits, molecular aspects, diagnostic techniques, and management of MAC. As our understanding of mucinous colorectal adenocarcinoma continues to evolve, future research may result in the creation of more targeted therapies and personalized treatment approaches.

Keywords: mucinous colorectal cancer, Microsatellite instability, rectal MRI, Targeted molecular therapy, Cytoreductive Surgery

1.Περίληψη: Το βλεννώδες αδενοκαρκίνωμα του παχέος εντέρου και του ορθού αποτελεί το 1.6-25.4% των περιπτώσεων κολορθικού καρκίνου και ορίζεται από την παρουσία εξωκυττάριας βλέννης σε ποσοστό πάνω από το 50% του όγκου της βλάβης. Η πρόγνωση του βλεννώδους αδενοκαρκινώματος συγκριτικά με το μη βλεννώδες αδενοκαρκίνωμα έχει υπάρξει αντικείμενο πολλαπλών ερευνών. Τυπικά, το βλεννώδες αδενοκαρκίνωμα του παχέος εντέρου και του ορθού διαγιγνώσκεται σε πιο προχωρημένο στάδιο, έχει μειωμένη ανταπόκριση στην χημειοθεραπεία και εμφανίζει μεγαλύτερο αριθμό διηθημένων λεμφαδένων και σε μεγαλύτερη συχνότητα περιτοναϊκές μεταστάσεις. Επιπλέον, η βλεννώδης διαφοροποίηση σχετίζεται με ιδιαίτερα μικροσκοπικά, μοριακά και επιγενετικά χαρακτηριστικά, όπως μεγαλύτερο ποσοστό μικροδορυφορικής αστάθειας (MSI), με το μονοπάτι του φαινοτύπου μεθυλίωσης των νησιδίων CpG(CIMP) και με μεταλλάξεις γονιδίων BRAF, συγκριτικά με τα μη βλεννώδη κολορθικά νεοπλάσματα. Παρόλα αυτά, οι σύγχρονες κατευθυντήριες οδηγίες δεν διαθέτουν ξεχωριστές συστάσεις προσαρμοσμένες στην διαχείριση του συγκεκριμένου παθολογοανατομικού υποτύπου κολορθικού καρκίνου. Σε αυτήν την ανασκόπηση της βιβλιογραφίας, στόχος είναι να συνοψίσουμε την επιδημιολογία, πρόγνωση, τα ιδιαίτερα κλινικοπαθολογικά και μοριακά χαρακτηριστικά, τα διαγνωστικά εργαλεία και την αντιμετώπιση του

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βλεννώδους αδενοκαρκινώματος του παχέος εντέρου και ορθού. Όσο η κατανόηση του βλεννώδους νεοπλάσματος γίνεται βαθύτερη και εξελίσσεται, μελλοντικές έρευνες πιθανόν να οδηγήσουν στην ανάπτυξη πιο στοχευμένων και εξατομικευμένων θεραπειών.

Λέξεις κλειδιά: βλεννώδες αδενοκαρκίνωμα, Μικροδορυφορική αστάθεια, MRI ορθού, Στοχευμένη μοριακή θεραπεία, Κυτταρομειωτική επέμβαση

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2. Introduction

2.1. Incidence of Colorectal Cancer

In 2020, colorectal cancer (including anal cancer) was estimated to have caused approximately 1.9 million new cases and 935,000 deaths, comprising nearly one-tenth of all cancer cases. Colorectal cancer ranks third in terms of incidence but second in fatality rates. Developed nations exhibit nearly four times higher incidence rates compared to developing countries, while mortality rates vary less due to higher mortality in transitioning countries. Globally, colon cancer incidence rates vary, with European regions, Australia/New Zealand, and North America demonstrating the highest rates. Hungary and Norway rank first in incidence among men and women, respectively. Rectal cancer incidence rates also vary by region, being highest in Eastern Asia. Conversely, colon and rectal cancer rates are typically low in Africa and Central South Asia [1].

By 2030, there will be an estimated 1.1 million additional fatalities and over 2.2 million new cases of colorectal cancer (CRC), marking a 60% increase in the disease's global burden compared to the incidence and mortality rates recorded in 2012, according to data from the GLOBOCAN database [2].

A significant proportion of colorectal cancer (CRC) cases (60-65%) occur spontaneously, meaning they develop in individuals without a family history of the disease or inherited genetic mutations that increase the risk. These cases result from acquired somatic genetic and epigenetic abnormalities primarily induced by modifiable risk factors. However, a hereditary component is present in 35–40% of CRC cases. Approximately 25% of CRC cases have a history of the illness in the family without any clear familial cancer syndrome. Only about five percent are connected to hereditary cancer syndromes, like familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome). These syndromes arise from inherited germline mutations in relatively rare but highly susceptible genes (APC and MLH1, respectively). It's essential to note that CRCs with heritable components are not solely genetic; environmental factors also contribute to carcinogenesis [3].

2.2. Carcinogenesis of Colorectal Cancer

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The natural history of colorectal cancer (CRC) encompasses four main stages: initiation, promotion, progression, and metastasis. Initiation, the first stage, is characterized by irreversible genetic damage, such as DNA adducts, which predisposes affected cells to subsequent neoplastic transformation. During the promotion phase, initiated cells proliferate and lead to aberrant growth, forming neoplasia. Subsequently, in the progression phase, benign tumor cells transition into malignant cancer cells, undergoing further genetic and epigenetic changes that confer them a selective growth advantage. Consequently, these cells acquire aggressive traits and the ability to spread. Metastasis, the final stage, involves the migration of cancer cells from the original organ to other organs or tissues via the lymphatic or circulatory systems. The duration of each phase varies greatly and is unpredictable; decades may be required to complete all stages of CRC. However, certain phases of CRC may progress more rapidly in cases of genetic diseases. Additionally, there is increasing awareness of the potential existence of cancer stem cells, which could contribute to colorectal carcinogenesis by continuously dividing into malignant cells or identical daughter cells, thereby generating a population of proliferative cancer cells [3].

Considering genetic heterogeneity, colorectal cancers seem to arise through multiple different mechanisms [4]. Three main genetic and epigenetic abnormalities play crucial roles in colorectal carcinogenesis: chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI). CIN is characterized by abnormalities in chromosome copy number and structure, including aneuploidy and polyploidy, which are believed to arise from errors during mitosis, such as deficiencies in mitotic checkpoint proteins and centrosome number. CIMP involves hypermethylation at repeating CG dinucleotides, known as CpG islands, within the promoter sequences of tumor suppressor genes (such as MLH1, MINT1, MINT2, and MINT3), leading to gene expression inhibition. There is currently no consensus on diagnostics and classification criteria for CIMP subtypes, and the underlying cause of CIMP remains unclear. Definitions of CIMP also vary significantly. MSI is defined by changes in the length of microsatellites, which are short nucleotide tandem repeats in DNA sequences. The primary cause of gene silencing in MSI is believed to be promoter hypermethylation, triggered by the functional loss of DNA mismatch repair genes like MLH1. These molecular phenotypes are not mutually exclusive, despite their distinct characteristics. The significant correlation between CIMP and MSI status stems from the fact that high levels of MSI result from CpG island hypermethylation, which inactivates DNA mismatch repair genes. Approximately 70% of CRCs with high MSI also exhibit high CIMP [3,4].

These molecular abnormalities accumulate during colorectal carcinogenesis in a non-random manner, with approximately 65-70% of sporadic colorectal cancer cases exhibiting CIN, 20% showing CIMP-positive

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status, and 15% displaying MSI-high status [3,4]. Furthermore, completely new paths are still being identified [4].

2.2.1. The sequence of adenoma to carcinoma

The adenoma-carcinoma sequence outlines the progression from precancerous polyps to colorectal cancer. These polyps, broadly classified as serrated or classic tubular adenomas, serve as the precursor lesions for the majority of colorectal cancers. Disruption of the regular processes governing DNA repair and cell division leads to the formation of adenomas. In the intestinal mucosa, constant renewal and proliferation occur primarily at the crypt base. As mutant cells migrate toward the intestinal lumen, the expected process of differentiation and subsequent apoptosis is disrupted, leading to the emergence of discrete adenomas. Over time, adenomatous polyps become larger and more dysplastic, potentially evolving into invasive tumors. Sequential alterations in crucial growth-regulating genes signal the transition from normal to hyperproliferative tissue, a progression proposed as a paradigm for solid carcinogenesis. Mutations in the adenomatous polyposis coli gene (APC), a tumor suppressor gene, or the BRAF oncogene, trigger the formation of regular adenomas or serrated polyps, respectively. The specific pathway employed determines the sequence of events. Further genetic changes mark the development of advanced polyps with high-grade dysplasia, eventually progressing to invasive tumors. However, not all adenomas progress to cancer; the onset of certain mutations in a specific order is necessary for malignancy to ensue. The exact tumorigenesis pathway dictates the timeframe. For example, tumor formation via the relatively faster microsatellite instability (MSI) pathway may occur within a few years, while carcinogenesis through the chromosomal instability (CIN) pathway may take ten years or longer [4].

2.2.2. The Chromosomal Instability (CIN) pathway

The chromosomal instability (CIN) pathway is characterized by chromosomal alterations such as somatic copy number alterations (SCNA), induced by aneuploidy, deletions, insertions, amplifications, or loss of heterozygosity (LOH). This pathway is observed in 65–70% of sporadic colorectal cancers, predominantly in distal colon cancer locations rather than proximal ones. Common mechanisms leading to CIN include chromosomal segregation defects, such as those governing sister chromatid separation, dysfunctional cell senescence due to telomere shortening leading to genomic reorganization, malfunctioning DNA damage-response machinery, and LOH at tumor suppressor genes [4].

The CIN pathway is typically associated with mutations in tumor suppressor or proto-oncogene genes, such as APC or KRAS, respectively. Specifically, in the typical adenoma-carcinoma sequence, the CIN pathway

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initiates with mutations in the tumor suppressor gene APC within the normal colonic mucosa. Subsequent alterations in genes like KRAS, SMAD4, and TP53 drive gradual differentiation into adenocarcinoma, leading to disruption of the Wnt/β-catenin, MAPK, PI3K, and TGF-β signaling pathways [5].

Further progression in carcinogenesis into intermediate and late stages involves BRAF mutations, accompanied by alterations in genes like TGFBR2, IGF2R, and BAX. These molecular changes contribute to the advancement of colorectal cancer along the CIN pathway [5].

2.2.3. The CpG island methylator phenotype (CIMP) pathway

CIMP, or CpG island methylator phenotype, is an epigenetic process that occurs prior to the development of malignancy. Increased methylation levels in the promoter regions are part of a mechanism that can silence tumor-suppressor genes. In colorectal cancer (CRC), epigenetic instability is characterized by hypermethylation of CpG islands, often occurring alongside hypomethylation of overall DNA. The hypermethylation of promoter sections of tumor suppressor genes is a common occurrence in CIMP-positive CRC, leading to the depletion of function associated with these genes [6].

In 1999, Toyota et al. identified CIMP as a mechanism in carcinogenesis [7]. Additionally, there is a significant overlap between CIMP tumors and microsatellite instability (MSI). High promoter methylation of several genes, including p16, MINT clones, THBS, and MLH1, is the hallmark of CIMP. CIMP is also associated with various clinicopathological, and molecular features, including more prevalence in female and older population, proximal tumors, MSI- high, and BRAF V600E mutations [6].

CIMP is classified into two groups: CIMP-low and CIMP-high, based on the amalgamation of genetic and epigenetic variability. DNA methylation profile analysis indicates that approximately 20% of CRCs are categorized as CIMP-high [6].

2.2.4. The Microsatellite Instability (MSI) pathway

As opposed to the chromosomal instability (CIN) pathway, colorectal tumors can also develop through hypermutable routes characterized by frequent somatic DNA base pair mutations, along with an elevated incidence of genomic copy number alterations. The key mechanism underlying this hypermutable behavior is the microsatellite instability (MSI) pathway [4].

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In general, alterations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or EPCAM (which encodes a protein regulating MSH2) lead to microsatellite instability. DNA microsatellites consist of repetitive nucleotide sequences, and errors can accumulate while DNA polymerase is binding to these repeated sequences, leading to frameshift mutations that result in shortened or non-functional proteins [4].

Under normal conditions, the mismatch repair mechanism detects and corrects these errors before daughter strand replication. However, in tumors with MMR gene mutations, the mismatched DNA is not repaired properly, allowing the cells to replicate with accumulated mutations, leading to a hypermutation phenotype [4].

MSI has been identified in about 15% of sporadic colorectal tumors and in nearly all colorectal tumors in patients with Lynch syndrome, the most common hereditary colon cancer syndrome caused by genetic variations in DNA MMR genes. However, the majority of MSI colorectal cancers are sporadic. The prevalent cause of the MSI phenotype is epigenetic silencing of the MLH1 gene by promoter hypermethylation. MSI phenotype colorectal cancers typically exhibit high levels of methylation at regulatory areas throughout the genetic code, such as the CpG island methylator phenotype (CIMP) [4].

Colorectal cancers with MSI phenotype often show less frequent APC and TP53 mutations but have a higher frequency of mutations in BRAF (particularly the BRAFV600E mutation), compared to those arising through the CIN pathway. However, colorectal cancers with MSI phenotype in Lynch syndrome patients typically do not have BRAF mutations [4].

In addition, the TGFB receptor-2 gene (TGFBR2), which encodes a protein that inhibits colon epithelial cell growth, is frequently mutated in MSI colorectal cancers, with more than 90% of them harboring mutations in TGFBR2 [4].

Several factors can trigger cancer through the MSI pathway. While APC mutations are present in a significant portion of MSI tumors, a distinct group of MSI cancers may arise after a BRAF mutation, sharing characteristics of both MSI and serrated neoplasia pathways. Colorectal cancers tend to grow faster through MSI than through the CIN route due to the hypermutable environment, with MSI-high cancers developing in 1-3 years instead of decades required by CIN tumors [4].

The NCI/Bethesda consensus guidelines define a standard panel of microsatellite locators to determine MSI status. Tumors with frameshift mutations in at least 30% of the marker genes are categorized as MSI-high,

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while those with frameshift mutations in less than 30% are classified as MSI-low. Tumors that do not exhibit instability are considered microsatellite stable (MSS). PCR and immunohistochemical analysis of MMR proteins are common methods for detecting MSI status, aiding in the identification of potential treatment targets for colorectal cancers. DNA sequencing can also be employed for MSI assessment [4].

2.2.5. The serrated neoplasia pathway

Over the past decade, research has delved into an alternative pathway to the typical adenoma-carcinoma pathway, characterized by the existence of serrated adenomas as lesions that precede. Early neoplastic serrated lesions contribute to 15 to 30% of all colorectal cancers. Histologically, these lesions are distinguished by the epithelial glandular crypts within the polyps exhibiting a "serrated" (or saw-toothed) appearance, initially considered benign. However, serrated lesions are connected to both synchronous and metachronous advanced colorectal cancers and are a significant contributor to "interval" colorectal neoplasia [5].

Serrated colorectal lesions scarcely exhibit APC mutations at the molecular level. While KRAS mutations remain less common, BRAF mutations, with variable incidence among different serrated subtypes, are prevalent in a large proportion of CRCs originating from serrated polyps. They are also linked to two genomic instability-related pathways: microsatellite instability (MSI) and the CpG island methylator phenotype (CIMP), with the latter considered the primary mechanism driving the irregular pathway towards CRC [5].

2.3. The Consensus Molecular Subtypes (CMS) of Colorectal Cancer

From a genetic perspective, colorectal cancer (CRC) is now recognized as a heterogeneous group of cancers originating within the same organ, rather than a single disease entity. Examples of this tumor heterogeneity include microsatellite instability (MSI) and CpG island methylation (CIMP). MSI is often associated with high levels of CIMP (CIMP-H) and is correlated with a more favorable prognosis for patients. Prognosis may be negatively impacted by the presence of BRAF or KRAS mutations; however, the adverse effects of BRAF mutations are mitigated in MSI-high tumors [8]. Additionally, factors such as tumor proliferation rates, stromal invasion, and immune system responses are now understood to play significant roles in tumor development. By utilizing these genetic and phenotypic characteristics to subtype CRC tumors, patients may receive more personalized treatment approaches [8].

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A consensus of four subtypes of CRC (CMS1: MSI Immune, CMS2: Canonical, CMS3: Metabolic, and CMS4: Mesenchymal) was proposed by Guinney et al. [8,9]. CMS1 CRC (14% of CRC cases) is characterized as an immune subtype with MSI, high CIMP, BRAF mutations, and high tumor infiltration of lymphocytes. CMS2 CRC (37% of CRC cases) is generally microsatellite stable (MSS), CIMP-negative, with low immune infiltration and high somatic copy number alterations (SCNA). CMS3 CRC (13% of CRC cases) is also MSS, with low CIMP, low SCNA, low immune infiltration, and characterized by KRAS mutations. Lastly, CMS4 CRC (23% of CRC cases) is MSS, CIPM negative, with normal immune infiltration and high SCNA. Overall, CMS1 CRC appears to have the best prognosis compared to the other types, while CMS4 has the worst prognosis [8]. Heterogeneous samples exhibiting combined features are categorized as mixed or indeterminate types (14% of CRC cases) [6]. Nevertheless, this classification cannot easily be incorporated into standard clinical pathology laboratories as they require specialized genetic testing [8,9].

2.4. Anatomical subtypes of colorectal cancer and their associations with tumor molecular features and other factors

Colorectal cancer (CRC) is a heterogeneous disease that originates in the large intestine, and each subtype exhibits variable causes and clinical outcomes. Traditionally, CRC subtypes have been characterized based on the tumor's anatomical location in three colorectal segments: proximal (caecum, ascending colon, hepatic flexure, and transverse colon), distal (splenic flexure, descending colon, and sigmoid colon), and rectal. Research indicates that risk factors for CRC vary among these anatomical subsites. For example, smoking has been associated with an increased risk of proximal and rectal cancer but not distal colon cancer. The microbial and host features of the large intestine may contribute to the etiological variability of CRC among tumor sites. As the colorectal axis progresses from the proximal colon to the rectum, pH, microbial loads, and short-chain fatty acid (microbial metabolites) abundance increase, potentially impacting colorectal carcinogenesis [3].

Proximal colon cancer is more common in women (34% vs. 25% in the European Prospective Investigation into Cancer cohort) and increases with age (35% for those under 60 and 60% for those over 70 in the USA). Proximal colon cancer is the most prevalent type both in white and black individuals (In the USA: 44% and 49% for the proximal; 27% and 26% for the distal; and 29% and 25% for the rectal, respectively). However, Asians have the highest percentage of rectal cancer (22% for proximal, 26% for distal, and 52% for rectal in Korea). Yet, CRC incidences were evenly distributed (about 32–34% for each subsite) among the segments

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of the colorectum among Asian-Pacific Islanders living in the United States. This fact implies that environmental variables might have a greater impact in the pathophysiology of colorectal cancer than genetic factors [3].

Interestingly, CRC molecular subtypes vary in distribution in the colon. MSI-high and CIMP-high subtypes are more prevalent in the proximal colon, while the CIN-positive subtype is more common in the distal colon [10]. Moreover, the Cancer Genome Atlas project, which profiled genomic changes in 20 cancer types, found that hypermethylation, MSI-high, CIMP-high, and BRAF mutations in the proximal colon were only found in hypermutated cancer (mutation rates >12 per 106 bases), accounting for 16% of CRC samples. Non-hypermutated CRC (mutation rates <8.24 per 106 bases) has frequent mutations in genes associated with the CIN-positive subtype, such as APC and TP53, as well as SOX9, which is linked to intestinal stem cell differentiation. Among non-hypermutated CRCs, colon and rectal tumors were indistinguishable at the genomic level. The results indicate that etiological heterogeneity by anatomical location of CRC may only apply to hypermutated cases. However, the study has the weak statistical power since the number of patients was less than 200 [11].

Regarding hereditary cancer syndromes, tumors in Hereditary Non-polyposis Colorectal Cancer (HNPCC) are mostly located in the proximal colon, whereas tumors associated with Familial Adenomatous Polyposis (FAP) predominantly develop in the distal colon [3].

2.5. Histological types of colorectal carcinoma

The majority of CRCs (>90%) are classified as adenocarcinomas, arising from epithelial cells in the colon mucosa. Other histologic variations of CRCs, as classified by the World Health Organization (WHO), include mucinous, signet ring cell, medullary, micropapillary, serrated, cribriform comedo-type, adenosquamous, spindle cell, neuroendocrine, and undifferentiated. Conventional adenocarcinoma is graded based on glandular development in histology. Well-differentiated adenocarcinoma consists of >95% gland-forming tumor. Moderately differentiated adenocarcinoma exhibits 50-95% gland development, while poorly differentiated adenocarcinoma is largely solid, with less than 50% gland development. Approximately 70% of CRCs are classified as moderately differentiated, with well and poorly differentiated carcinomas accounting for 10% and 20%, respectively [12].

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3. Mucinous Adenocarcinoma

3.1. Introduction to Mucinous adenocarcinoma

Historically, various descriptive terms such as colloid carcinoma, gelatinous carcinoma, and degenerative carcinoma have been utilized to characterize the mucin-generating phenotype in colorectal cancer [13]. According to the WHO, colorectal mucinous carcinoma is defined by the presence of extracellular mucin in more than 50% of the tumor volume. Tumors with a substantial mucinous component (more than 10% but less than 50%) are commonly categorized as adenocarcinoma with mucinous characteristics or mucinous differentiation. Based on this definition, mucinous adenocarcinoma accounts for 1.6-25.4% of all colorectal malignancies [12, 13].

Mucinous adenocarcinoma is characterized by massive glandular structures containing pools of extracellular mucin, with varying numbers of specific tumor cells, like signet ring cells. The prognosis of MAC compared to typical adenocarcinoma has been debated in various studies. Many mucinous carcinomas occur in individuals with hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) and are hence MSI-high tumors, with low-grade behavior. In contrast, MACs that are microsatellite stable (MSS) are likely to be more aggressive, especially when diagnosed at an already advanced stage [12].

Mucinous differentiation is associated with specific microscopic, molecular, and (epi)genetic traits. Mucinous tumors exhibit increased expression of the mucin gene MUC2, as well as ectopic expression of the gastric mucin MUC5AC, regulated by the transcription factor SOX2.5. Recent findings suggest that MUC2 overexpression in mucinous adenocarcinoma is mediated by hypomethylation of the MUC2 promoter. Upregulation of MUC2 expression is also linked to the transcription factor HATH1. Mucinous adenocarcinoma is associated with higher microsatellite instability (MSI), CpG island methylation phenotype, BRAF mutation, and trefoil factor 1 expression compared to non-mucinous CRC. However, it is associated with lower P53 expression, APC mutation rate, and p21 expression. Moreover, there have been conflicting reports on the rate of KRAS mutation and apoptotic activity in mucinous adenocarcinoma versus non-mucinous CRC [13].

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All these characteristics that are more prevalent in mucinous colorectal cancer may be the key to understand the behavior and prognosis of this particular type of cancer and could be the key to new targeted molecular treatment approaches in the future.

3.2. Prognosis of mucinous colorectal cancer

According to studies by Ott C. et al. and Catalano V. et al., patients with MAC exhibit a lower 3-year progression-free survival rate when compared to non-mucinous (56.9% vs. 79.2%, respectively) and a shorter median overall survival (48.4 months vs. 60.2 months, respectively) [14, 15]. Nevertheless, other studies have suggested that the histology of MAC is not related to the prognosis. A population-based study involving nearly 120,000 colon cancer patients in Europe found that mucinous histology had no adverse impact on survival [16]. On the contrary, Japanese researchers discovered that MAC was associated with a worse survival rate in patients with stage III and IV cancers compared to non-mucinous tumors [17]. Additionally, according to Hugen et al., a poor prognosis for MAC was observed only in rectal cancer and not in colon cancer [18]. Moreover, when adjusting for the stage of presentation, a meta-analysis of 44 studies involving over 220,000 patients revealed a worse prognosis for individuals with MAC histology. More particularly, mucinous differentiation carries a 2-8% increased risk of death, a risk that persists even after adjusting for the disease stage [13]. Currently, there is no established prognostic value of mucinous colorectal adenocarcinoma when considering factors such as tumor site, molecular alterations, population features, or alternative treatment strategies [19].

3.3. Clinicopathologic characteristics of mucinous colorectal cancer

Adenocarcinoma is the most frequent histologic subtype of colorectal cancer (CRC), with MAC representing a unique subtype defined by significant mucinous components comprising at least 50% of the tumor mass. Several studies conclude that 1.6-25.4% of all colorectal cancer patients have mucinous adenocarcinomas. However, this rate appears to be higher in Western nations and lower in Asian nations. Moreover, MAC is more frequent in the right colon than in the rectum or left colon [19].

Compared to non-mucinous, MAC appears more often in females and younger individuals. Additionally, mucinous colorectal adenocarcinomas are typically diagnosed at an advanced stage and tend to respond less effectively to chemotherapy [19]. Furthermore, mucinous colorectal cancer exhibits a higher rate of lymph

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node involvement and peritoneal implantation, as well as a significantly larger maximal size compared to non-mucinous colorectal adenocarcinoma [14].

3.4. Molecular pathogenesis and genetic factors associated with Mucinous Adenocarcinoma

Mucinous colorectal cancers are associated with various molecular alterations that influence their incidence and prognosis [19]. Mutations in the APC gene, indicative of chromosomal instability, are rare in MAC. Additionally, p53 mutations are more frequent in chromosomal instability-related cancers than in mucinous colorectal cancer. Furthermore, alternative mechanisms leading to CRC carcinogenesis have been identified, including incorrect methylation and silencing of tumor suppressor genes, known as epigenetic instability, and promoter methylation of the MLH1 gene, which leads to sporadic microsatellite instability [19,20,21].

A meta-analysis conducted by Reynolds et al. in 2019, which included 46 papers comprising 17,746 patients, shed light on the molecular correlations of MAC. This study indicated that microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and KRAS and BRAF mutations are all positively correlated with mucinous colorectal cancer (CRC). Conversely, alterations in p53 expression are inversely correlated [20].

The RAS/MAPK pathway, which includes both BRAF and KRAS, plays a crucial role in cell proliferation and apoptosis regulation. KRAS mutations cause an epidermal growth factor receptor-independent disruption of the RAS/RAF/MAPK pathway, which controls cell proliferation and survival and is an indicator of prognosis in CRC. BRAF mutations are typically found in patients with MAC and have been connected to an infiltrative tumor development pattern [19,20,21].

Alongside with KRAS and BRAF mutations, a higher incidence of mutations in the PI3K/AKT pathways has been identified in patients with MAC. Alterations in the phosphoinositide 3-kinase (PI3K) pathway affect cellular development, metabolism, proliferation, and apoptosis, all of which play a significant role in the etiology of many malignancies. In a mouse model, Leystra et al. demonstrated that the expression of a predominantly active version of the PI3K protein contributes to the formation of mucinous colon carcinomas [22] These findings support the idea of a distinct oncogenic pathway resulting in MAC carcinogenesis compared to the conventional adenoma-carcinoma sequence {20,21,22].

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3.4.1. Microsatellite instability (MSI) in mucinous colorectal cancer

Microsatellite instability (MSI) plays a crucial role in the pathogenesis and prognosis of MAC. MAC exhibits a higher rate of MSI-high than non-mucinous CRC. As it has already been mentioned, while the majority of colorectal cancer (CRC) cases are related to chromosomal instability (CIN), approximately 15% are MSI-high. Among these 15% of all CRC cases, 12% are sporadic, and 3% are associated with Lynch syndrome [19]. According to Hugen et al., MAC accounts for 22%-40% of Lynch syndrome-related CRC cases, suggesting a link between the two conditions [23].

Patients with MAC and MSI have been observed to have higher survival rates compared to those with microsatellite stable (MSS) tumors. MSI-high is connected to a lower risk of metastasis to regional lymph nodes or distant organs in CRC compared to low-frequency microsatellite instability (MSI-low), and suchlike outcomes have been observed regarding recurrence rates [24]. According to a study by Andrici et al., patients with mucinous MSI/MMR-deficient CRC have shown substantially greater 5-year survival rates compared to non-mucinous MSI- high CRC patients (73% vs. 53%, respectively) or mucinous MSS/MMR-proficient patients (73% vs. 57%, respectively) [25].

Three molecular alterations have been identified as potential causes of MSI. First, alterations in mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2) may cause MSI due to insufficient MMR system function, leading to genetic hypermutability and MSI-related malignancies such as Lynch syndrome-correlated CRC [26]. Second, CpG island methylator phenotype (CIMP) is connected to MSI in sporadic CRC. Hypermethylation of CpG islands in the promoter sections of tumor suppressor genes, such as MLH1, can silence these genes, contributing to oncogenesis suppression [19]. Third, mutations in genes of the RAS/MAPK pathway, like the v-Ki-ras2 (KRAS) and B-Raf proto-oncogene (BRAF), can cause MSI. The activation of the RAS/MAPK pathway increases cell proliferation and decreases cell apoptosis [27]. KRAS-mutated carcinomas, which are more frequent in the right colon, exhibit also a higher frequency of mucinous differentiation [28]. Moreover, KRAS mutations occur more frequently (65%) in malignancies with high mucin production than in malignancies with low mucin production [29]. Additionally, mucinous adenocarcinoma pathology is observed more frequently in BRAF mutant tumors compared to BRAF wild-type and KRAS/BRAF wild-type cancers. Patients with BRAF mutations have been found to exhibit significantly shorter median overall survival (11.0 months versus 40.6 months) compared to those with BRAF wild-type tumors, and they are often associated with unfavorable histological characteristics [30, 31].

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The BRAF V600E mutation has garnered attention in recent studies due to its significance in MSI status and its prognostic implications. This mutation is estimated to be responsible for about 80% of MSI cases and is associated with characteristics such as proximal tumor site and mucinous histology. There is a substantial correlation between the BRAF V600E mutation and sporadic cases of MSI-high patients [32, 33].

In summary, mutations in the RAS/MAPK pathway genes, particularly BRAF mutations such as BRAF V600E, are more likely to result in MSI and may be associated with mucin production, location of the tumor in the right colon, and the histology of MAC [19]. These molecular alterations contribute to the unique characteristics and prognosis of mucinous colorectal adenocarcinoma.

3.4.2. Vascular Endothelial Growth Factor (VEGF) in mucinous colorectal cancer

Vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis, which is the formation of new blood vessels, and it is implicated in both primary and metastatic colorectal cancer (CRC). Elevated levels of VEGF are often found in poorly differentiated or mucinous adenocarcinomas. Given the significance of VEGF in CRC, targeted therapies that inhibit VEGF signaling have been developed. Bevacizumab, a monoclonal antibody that targets VEGF, is commonly used in combination with chemotherapy as a first- or second-line treatment for individuals with metastatic mucinous colorectal cancer. This combination therapy helps to suppress angiogenesis and tumor growth [19].

In cases where bevacizumab is ineffective or disease progression occurs, other VEGF-targeted therapies may be considered. Regorafenib and fruquintinib are multikinase inhibitors that also target VEGF receptors. They are typically used as monotherapy in later lines of treatment, such as third-line therapy, for patients with advanced CRC who have already received prior chemotherapy and targeted therapy [19].

Overall, targeting VEGF signaling pathways has become an important strategy in the treatment of mucinous colorectal cancer, helping to improve outcomes and prolong survival in affected individuals.

3.4.3. Mucinous colorectal cancer and mucin expression

The expression and regulation of mucins, particularly MUC2, play crucial roles in the pathogenesis and characteristics of mucinous colorectal cancer (CRC). Mucins are glycosylated proteins that are either

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secretory or transmembrane, serving to protect the colonic epithelium and modulate inflammatory responses. MUC2, MUC5AC, MUC5B, and MUC6 are secreted mucins that create a mucous gel that coats epithelial surfaces. MUC1, MUC4, MUC13, and MUC16 are transmembrane mucins, which traverse the cell membrane, permitting exterior glycosylated structures and transmembrane domains to engage with intracellular functions [21].

MUC2 is a secreted mucin that is a major component of intestinal mucus, particularly in the proximal colon where mucinous CRCs are more prevalent. Furthermore, when mucinous CRC is compared to non-mucinous CRC, the expression of MUC5AC, which is found on the same chromosome as MUC2, is enhanced. The presence of MUC2 and/or MUC5AC has been linked to right-sided mucinous CRC. MUC2 overexpression is a defining feature of MAC. On the contrary, MUC2 expression is frequently reduced in non-mucinous CRC. MUC2 deficiency is linked to enhanced intestinal epithelial cell proliferation in response to inflammatory conditions. MUC2's role in inflammation and tumor suppression may look contradictory when MUC2 expression is enhanced in MAC [34].

Several factors influence MUC2 expression in the colonic epithelium. Okudaira et al. observed that methylation of the MUC2 gene promoter, for example, is lower in MAC lines compared to non-mucinous ones, and it correlates with increased mucin production. Additionally, MUC2 expression is downregulated when functioning p53 is lost. In several cell lines, the p53 protein regulates MUC2 expression through transcription. MUC2 regulation by p53 coincides with the observation of lower rate of p53 mutations in MAC with higher MUC2 expression. Non-mucinous CRC, on the other hand, has a high rate of p53 mutation along with decreased MUC2 expression [34].

Furthermore, MUC2 gene transcription is regulated by the mitogen-activated protein kinase (MAPK) signaling pathway. Activation of MAPK signaling, often associated with KRAS mutations and persistent inflammation, is characteristic of mucinous carcinoma. This suggests a potential link between oncogenic signaling pathways and mucin expression in CRC [20,21,22,34].

Interestingly, while MUC2 overexpression is a defining feature of mucinous CRCs, it has been proposed that this may reflect the cancer cells' ability to produce mucin rather than mucin's intrinsic action. Additionally, alterations in mucin expression in malignancies may be influenced by epigenetic pathways or may serve as a mechanism for immune evasion by cancer cells [20,21,22,34].

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Overall, understanding the regulation and expression of mucins, particularly MUC2, provides insights into the development and behavior of mucinous colorectal cancer and may offer potential targets for therapeutic intervention.

3.5. Diagnosis of Mucinous Colorectal Cancer

Nowadays, diagnosing mucinous adenocarcinoma of the colon typically involves various imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), along with postoperative pathological evaluation [35].

On CT scan, MAC is characterized by thickening of the intestinal wall and the presence of low-density cystic lesions. Additionally, arterial phase enhancement is typically not significantly increased compared to normal tissue [19]. A study by Li et al. observed that mucinous adenocarcinoma had a higher incidence (37.2% vs. 11.5%, P,0.001) and more severe eccentric bowel-wall thickening (6.29±2.69 cm vs. 4.57±1.74 cm, P,0.001) in CT scan compared to conventional adenocarcinoma [36]. Moreover, mucinous adenocarcinoma often exhibits also higher rates of heterogeneous contrast enhancement and more lessions with hypoattenuation. Lastly, intratumoral calcifications were more frequent in mucinous colorectal cancer when compared to adenocarcinoma and signet-ring cell carcinoma [36, 37].

MRI can also aid in the differentiation between mucinous and non-mucinous adenocarcinoma. Mucin typically appears with low signal intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging, which is equal to or greater than the rectum fat signals, while non-mucinous adenocarcinomas display intermediate signal intensity on T2-weighted imaging [35].

PET imaging, particularly with fluorodeoxyglucose (FDG), is utilized in complicated cases to assess for metastatic disease. However, mucinous tumors may show poor FDG uptake because PET tumor FDG avidity interacts inversely with mucin levels potentially leading to false-negative results [38]. Nonetheless, a more recent study of Dalton et al. about rectal cancer indicated that both mucinous and non-mucinous rectal tumors exhibit equivalent 18F-FDG uptake during PET/CT imaging [39]. Considering the above, PET/CT is not proven a reliable enough tool to evaluate a mucinous neoplasm. Therefore, a negative PET result ought to be interpreted carefully [35].

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Ultimately, postoperative pathological evaluation remains the most accurate diagnostic tool for mucinous adenocarcinoma since the whole volume of the tumour is being evaluated for the presence of mucous. Mucinous adenocarcinomas are defined by the presence of extracellular mucin comprising more than 50% of the tumor volume. Therefore, accurately assessing mucin concentration in preoperative biopsies, where the sample size may be limited, can be challenging [40].

3.5.1. Significance of Rectal MRI in mucinous rectal cancer

Mucinous rectal carcinomas are associated with distinct characteristics compared to cancers of the proximal colon. They are less likely to exhibit DNA microsatellite instability (MSI) and have a poorer prognosis, often presenting with more widespread invasion at the time of diagnosis than the non-mucinous subtype. The production of mucus by these tumors under pressure facilitates tissue plane division in the intestinal wall, granting greater access to the peritoneal cavity. Additionally, the fluid produced by mucinous rectal carcinomas can be drawn into lymphatic vessels, contributing to tumor spread to regional lymph nodes. Due to their ability to infiltrate the outer rectal wall easily, mucinous rectal carcinomas may appear as perirectal cystic tumors. Therefore, understanding the imaging characteristics of these tumors is crucial for radiologists and surgeons to establish an appropriate treatment plan [40,41].

The status of the circumferential resection margin (CRM) has emerged as a crucial prognostic factor for local recurrence following primary total mesorectal excision (TME) surgery in patients with rectal cancer. Preoperative magnetic resonance imaging (MRI) has demonstrated its ability to accurately predict the CRM status, aiding in treatment planning [41,42].

Studies have shown that patients with positive CRM status following neoadjuvant therapy have a significantly higher risk of local recurrence compared to those with negative CRM status. For instance, Gosens et al. reported a local recurrence rate of 43% in ypCRM-positive patients compared to 8% in ypCRM-negative patients [42]. Similarly, Mawdsley et al. observed local recurrence in 62% of ypCRM-positive patients compared to 10% in ypCRM-negative patients [43]. These findings underscore the importance of CRM status as a prognostic indicator for local recurrence following neoadjuvant treatment.

Given the implications of CRM status on treatment outcomes, it is essential to consider potential risk factors for decreased treatment response in patients with potentially involved resection margins during pretherapeutic diagnostic evaluations. Preoperative MRI plays a crucial role in this regard by accurately

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predicting CRM status, thereby enabling clinicians to individualize therapy and optimize treatment strategies based on the patient's risk profile. By tailoring treatment approaches to the patient's specific circumstances, including CRM status, clinicians can strive to improve outcomes and minimize the risk of local recurrence in rectal cancer patients undergoing neoadjuvant therapy and TME surgery [41, 42, 43].

Moreover, preoperative magnetic resonance imaging (MRI) plays a significant role in evaluating tissue characteristics and can accurately identify mucin pools within rectal carcinomas with an accuracy rate of 97% along with substantial interobserver agreement attributed to the high signal intensity in T2-weighted imaging [40, 41]. MRI can estimate the amount of extracellular mucin in the tumor, aiding in the diagnosis of mucinous carcinoma and allowing for preoperative or retrospective assessment of the entire tumor volume. This capability of MRI is particularly valuable when a thorough examination of the entire tumor mass may be challenging during preoperative pathological evaluation [40].

According to a study of Oberholzer et al., patients suffering from mucinous carcinoma experienced a significantly increased risk of incomplete resections(R1) following chemoradiation. Furthermore, only mucinous carcinomas showed signs of progressing disease. Thus far, the findings reflect reports of poor treatment response in mucinous carcinomas. This study, demonstrates that the mucinous status at the pretherapeutic MRI has a significant prognostic value. Nevertheless, only 88 patients were included in the study, which is a considerable small amount. Larger studies are needed to fully assess the prognostic implications of mucinous status determined by MRI [41].

Developing tests, such as preoperative MRI, to predict response to therapy aims to tailor treatment intensity based on disease risk. While phase I/II trials have investigated intensified multimodal therapy regimens, including adding irinotecan or oxaliplatin to fluoropyrimidines and increasing radiotherapy intensity, questions remain about their effectiveness and associated elevated toxicity and mortality.

Furthermore, mucinous histology has been associated with poorer response to 5-fluorouracil in advanced colorectal cancer and varying levels of resistance to methotrexate and/or fluoropyrimidine in vitro. Therefore, individually intensified treatment approaches using innovative medications, hypofractionation, or modified chemotherapy may be beneficial for patients with mucinous carcinoma identified through pretherapeutic MRI. However, further research is needed to explore these possibilities [41].

3.6. Treatment of Mucinous Colorectal Cancer

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Despite the recognized molecular and histological differences between MAC and non-mucinous colorectal adenocarcinomas, current clinical guidelines recommend that individuals with mucinous colorectal adenocarcinoma follow the standard treatment protocols established for colorectal adenocarcinomas in general. These treatment protocols typically rely on factors such as TNM staging, biomarkers including BRAF, RAS, HER2, and microsatellite status, among others [19, 35].

TNM staging remains a fundamental aspect of treatment decision-making, providing valuable information about the extent of the tumor, the involvement of nearby lymph nodes, and the presence of distant metastases. Biomarkers such as BRAF, RAS, and HER2 status help guide treatment choices, as they can influence response to targeted therapies and prognosis. For instance, BRAF mutations are associated with a poorer prognosis and resistance to certain treatments, while RAS mutations can affect response to anti-EGFR therapies. Microsatellite status, particularly microsatellite instability-high (MSI-H), is also an important biomarker that can impact treatment decisions, as MSI-H tumors are more likely to respond to immunotherapy.

While mucinous colorectal adenocarcinomas may exhibit distinct histological and molecular features, such as higher rates of MSI and BRAF mutations, current clinical guidelines do not provide specific recommendations tailored to this subtype. Instead, treatment decisions are based on established factors such as TNM staging and biomarker status, which are essential for guiding personalized treatment strategies and optimizing patient outcomes. As our understanding of mucinous colorectal adenocarcinoma continues to evolve, future research may result in the development of more targeted treatments and personalized approaches for this patient population.

3.6.1. Surgical Treatment

Multimodal CRC treatments are becoming increasingly crucial. There are now several ways to treat colorectal cancer, including immunological therapy, radiation, chemotherapy, and molecular targeted therapy. However, the most effective approach to obtain a radical cure for CRC is still the surgical resection [44].

Richard John Heald introduced total mesorectal excision (TME) in 1979, revolutionizing rectal cancer surgery. The concept of TME involves the meticulous dissection and removal of the entire mesorectum, including the pararectal lymph nodes and surrounding fascia. Heald outlined the sequential steps of TME, which include ligating the inferior mesenteric artery at its origin, mobilizing the left colic flexure,

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transecting the left-sided colon at the junction of the descending and sigmoid colon, dividing the lymphatic vessels and middle rectal vessels ventrolaterally at the level of the pelvic floor, and incorporating all pelvic fat tissue and lymphatic structures. This precise dissection is achieved by carefully navigating the avascular plane in the pelvis, ventral to the presacral fascia (of Waldeyer), and outside the visceral fascia of the rectum, known as the 'holy' plane [45]. Even after 40 years, TME remains the gold standard procedure in rectal cancer surgery [46].

Similarly, concepts like extended (D3) lymphadenectomy and complete mesocolic excision (CME) have garnered attention in colon cancer surgery. In 2009, Dr. Hohenberger and colleagues proposed CME as a method akin to TME for colon tumors. However, widespread acceptance of CME in colon cancer surgery has not been achieved, unlike TME in rectal cancer surgery. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) established selective D3 lymphadenectomy as a standard procedure for colorectal cancer by the late 1990s, involving meticulous dissection of the visceral fascia to remove a complete mesocolic "envelope" with the specimen. By 2010, a D3 dissection was performed in almost 75% of all colon resections for stage II or III illness performed nationally in Japan [47]. In spite of the fact that D3 dissection is recommended by the JSCCR, routine extended lymphadenectomy is not advised in the United States, as per the American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines published in 2022. The ASCRS recommends judicious dissection of only suspicious lymph nodes outside the usual resection field [48]. On the contrary, the D3 dissection is advised by the 2019 JSCCR recommendations in light of preoperative imaging, intraoperative results, and/or the extent of tumor invasion [49].

Concluding, based on current literature, CME with D3 dissection may be considered in selected patients, particularly those with aggressive colon tumors, unfavorable tumor biology, and a high likelihood of apical lymph node (ALN) involvement. For left-sided colon malignancies, CME with central vascular ligation (CVL) is standard, while for right-sided colon cancers, the use of CME with D3 dissection remains debatable. Decisions regarding CME and D3 dissection should consider patient characteristics, preoperative imaging, precise tumor biology and location, and lymphovascular anatomy. While ongoing clinical trials explore the long-term outcomes associated with CME and/or D3 dissection, efforts should be made to standardize preoperative imaging and postoperative pathology, develop tailored treatment regimens based on tumor genotypes and phenotypes, and provide surgeons with comprehensive training to manage complex locally advanced colon cancers. Achieving the true gold standard in colon cancer surgery necessitates optimization of every aspect of the treatment process [50].

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3.6.2. Laparoscopic Surgery for mucinous colorectal cancer

Better short-term results, including reduced intraoperative blood loss, reduced postoperative pain, increased likelihood of satisfactory resection quality, faster postoperative recovery, and a shorter hospital stay, are provided by laparoscopic surgery. Nonetheless, some studies indicate that laparoscopic treatment for pathological T4 colorectal cancer is still debatable. In the meanwhile, further proof of the long-term effects of laparoscopic surgery is required [44, 51].

Numerous studies have examined the benefits and drawbacks of laparoscopic surgery in comparison to open surgery for colorectal cancer, but only one specific study of laparoscopic treatment for MAC has been found in the existing literature. When compared to the non-mucinous subtype, MAC exhibits a greater ratio of peritoneal implant to lymph node infiltration [52]. Furthermore, compared to patients with AC, those with MAC typically have tumors of a more advanced T stage. This may indicate an increased risk of local extension, which lowers the chances of both complete and curative resection [53]. Moreover, it is possible for undetectable peritoneal metastases (not identified by imaging) to exist, particularly in the T4 stage of MAC. In addition, surgical therapy for MAC presents a problem in preventing gelatinous MAC from leaking into the abdominal cavity during the procedure. The complexity of laparoscopic procedures and the pneumoperitoneum tend to complicate this problem [44].

Qing et al. conducted the only retrospective analysis in the PubMed database that compared laparoscopic and open treatment for mucinous colorectal cancer. Limitations of the study included a limited sample size and the retrospective character. The study included 162 patients with mucinous colorectal carcinoma in stages I, II, or III. Finally, the study's outcomes demonstrated that laparoscopic surgery for MAC is a safe and technically feasible choice, with no statistical difference between laparoscopic and open treatment in terms of disease-free survival or overall survival rates [44]. However, more extensive, multicenter, and randomized controlled trials are needed to elucidate the impact of mucinous pathology on CRC treatment outcomes.

3.6.3. Impact of surgery in prognosis of mucinous colon cancer with liver metastases

The prognosis of patients with mucinous colon cancer and liver metastases (M-CLM) remains a subject of debate due to variations in treatment approaches for metastatic disease. Although surgery offers better survival outcomes for selected patients with colon cancer liver metastasis (CLM), fewer than 20% of M-

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CLM patients meet the criteria for resectability [54, 55]. The liver is the most common site of metastases in colorectal cancer, with M-CLM tumors often exhibiting metastases to other sites, contributing to the complexity of management decisions. Incomplete resection is associated with poor survival and high recurrence rates, underscoring the need for effective treatment strategies [55, 56, 57, 58].

Despite the elevated risk of recurrence, the limited response of metastatic mucinous colon cancer to chemotherapy suggests a potential role for surgery in improving outcomes [13, 55, 59]. However, conflicting evidence exist regarding the impact of surgery on M-CLM patients' prognosis compared to those with adenocarcinoma of the colon and liver metastases (A-CLM). Some studies suggest comparable survival between stage IV MAC patients undergoing surgery and those with adenocarcinoma, while others indicate worse outcomes for M-CLM patients after complete resection [56, 60].

The role of surgery in M-CLM patients who are not candidates for radical resection remains poorly understood, highlighting the need for further research. A retrospective study by Huang et al. involving 5816 patients with colon cancer and liver metastases investigated the outcomes of M-CLM patients undergoing surgery compared to those receiving no treatment. The study found that surgery was associated with significantly higher overall and cancer-specific survival rates for M-CLM patients compared to non-treatment groups, although outcomes were still inferior to A-CLM patients undergoing surgery. Partial colectomy for the primary site resulted in comparable or improved survival outcomes for M-CLM patients compared to hemicolectomy, emphasizing the importance of surgical intervention in this population [55].

Moving forward, well-designed multicenter retrospective and prospective studies are needed to further elucidate the impact of surgery on the prognosis of M-CLM patients and inform treatment decisions for this challenging patient population.

3.6.4. Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in mucinous colorectal cancer

The treatment of metastatic peritoneal disease in colorectal cancer has evolved over the years, with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) being proposed as a combined approach by Sugarbaker et al. in 1995. This approach aims to surgically remove visible macroscopic disease and eliminate any residual disease, making it particularly relevant for patients with MAC who have a higher rate of peritoneal dissemination [61, 62].

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However, recent evidence from a multicenter, randomized clinical trial has questioned the benefit of adding HIPEC to CRS for patients with peritoneal metastatic colorectal cancer. These studies have shown that HIPEC did not improve outcomes and was associated with a higher frequency of postoperative complications. Therefore, CRS alone has emerged as the cornerstone of treatment for colorectal peritoneal disease [63].

The decision to pursue CRS plus HIPEC should be based on a comprehensive and personalized evaluation, taking into account factors such as the peritoneal cancer index, prior chemotherapy history, and performance status scores of the patient. This approach ensures that treatment decisions are tailored to individual patient characteristics and optimize the chances of successful outcomes [64].

Furthermore, the existing literature has not given much consideration to tumor characteristics and histological subtypes in the framework of multimodal therapy. In a study published in the relevant literature, Helold et al. compared the survival rates of patients with synchronous and metachronous peritoneal metastases, with a particular emphasis on mucinous adenocarcinoma treated with intraoperative HIPEC after CRS. This comparison was not previously explored. Patients with synchronous peritoneal metastases and MAC had the worst outcome, whereas patients with metachronous peritoneal metastases exhibited survival patterns akin to those of non-mucinous groups. The link connecting mucinous adenocarcinoma and advanced disease characteristics, such as elevated peritoneal cancer index (PCI) values and the requirement for more extended surgical treatments, like splenectomy and peritonectomy of right upper quadrant, left upper quadrant, and omental bursa, was also underlined by the study. However, the study has considering limitations since it was retrospective and included only a total number of 218 patients with peritoneal metastases [65].

Looking ahead, future research in peritoneal cancer should explore the translational prospects offered by CRS, which may open up new avenues of investigation and therapeutic strategies for this challenging disease. By focusing on personalized treatment approaches and leveraging the insights gained from CRS, researchers can continue to improve outcomes for patients with colorectal peritoneal metastases.

3.6.5. Chemotherapy and Resistance to cell death mechanisms in MAC

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Resistance to chemotherapeutic drugs in mucinous colorectal cancer (CRC) involves several proposed mechanisms, including physical barriers created by mucous around tumor cells, overexpression of mucin glycoproteins inhibiting apoptosis, genetic variations in drug metabolism genes, and alterations in the tumor immune microenvironment.

The physical structure of mucinous tumors, characterized by mucous surrounding tumor cells, can act as a physical barrier to chemotherapy administration. The response to adjuvant therapy may differ between patients with advanced-stage disease who have solid metastases protected by extracellular mucin and patients with micrometastases without this barrier. In cases with larger solid metastases, inadequate microvasculature due to mucous around the tumor may hinder chemotherapy administration and response. Moreover, the bulky mucinous tumor's compressing forces on the penetrating circulatory system may limit drug delivery to the tumor [66].

Another mechanism proposed to contribute in the resistance to cell death are the mucin glycoproteins which are overexpressed in mucinous colorectal cancer. Particularly, mucin glycoproteins can suppress apoptosis in in vitro as well as in vivo models of CRC, with various mechanisms including the inhibition of mitochondrial apoptotic signaling and the inhibition of death receptors [21].

Genetic variations in drug metabolism genes also play a role in chemotherapy resistance in MAC. [21]. Drug-resistance genes in mucinous and non-mucinous CRC differ significantly in terms of somatic mutation rates and copy number variation [67]. Glasgow et al. compared the expression of identified drug metabolism genes in 21 individuals with MAC to 30 patients with non-mucinous CRC. Mucinous tumors overexpress thymidyl late synthase (TYMS) and glutathione S-transferase p1 (GSTP1) genes, however there is no significant difference in drug-related gene expression in the research cohort [68]. A recent investigation of The Cancer Genome Atlas dataset discovered significant differences in the rate of simple somatic mutations and copy number variation in genes linked to chemotherapeutic drug resistance in MAC and non-mucinous cancers [21, 67]. Thymidine phosphorylase (TYMP), a gene linked to 5-FU resistance, had a higher simple somatic mutations rate in mucinous tumors (5.97%) compared to non-mucinous tumors (1.08%). Moreover, mutations in two genes linked to oxaliplatin resistance were more common in mucinous compared to non-mucinous tumors. Mutations in ATPase copper transporting beta were found in 8.96% of MACs, compared to 3.45% in non-mucinous tumors. Likewise, only 3.23% of non-mucinous cancers had a mutation in SRSF protein kinase 1 (SRPK1), compared to the 10.45% of mucinous cancers. These results could account for some of the differences in chemotherapy response between patients with

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and without mucinous colorectal cancer. Therefore, identifying and targeting genetic variations may improve chemotherapy sensitivity or provide a more tailored approach to adjuvant treatments [21, 67].

The tumor immune microenvironment of MAC may also contribute to chemotherapy resistance. The high extracellular MUC2 protein in mucinous CRC can function as a physical barrier to immune infiltration, inhibiting the immune response against the tumor. In addition, the mucin layer contains adhesion ligands and inhibitory cytokines. Moreover, the tumor microenvironment may inhibit antigen-presenting cells from initiating immune responses or effector cells from killing tumor cells [69]. Therefore, the immunological characteristics of mucinous CRC have received scant attention in the literature. In a study of 152 CRCs, Tozawa et al. observed that peri-tumoral lymphocyte infiltration was present in just 0-4% of mucinous CRCs, compared to 17% of non-mucinous CRCs [70]. The distribution of tumor CD8+ lymphocytes and stromal CD8+ lymphocytes in CRC with mucinous features, however, was not different, according to another recent investigation [71]. In solid tumors, high-density macrophage infiltration is linked to a poor prognosis. M2 differentiated macrophages promote tumor migration, invasion, and suppress anti-tumor immunity. Mucinous colorectal cancer has been linked to pan-macrophage, M1 macrophage, and M2 macrophage infiltration, according to a meta-analysis of four investigations [72].

Considering the immunological profile of MAC and the possibility of immune checkpoint suppression as a treatment approach, recent research has brought up an intriguing subject. Mismatch-repair deficiency predicts solid tumor response to immune checkpoint inhibition, leading to approval of immune checkpoint drugs for MSI high metastatic CRC treatment. MSI or inadequate mismatch repair causes significant neoantigen load and enhanced immunogenicity in MSI malignancies. [73]. Mucinous colorectal cancer has been linked with higher rates of MSI compared to non-mucinous subtype. Furthermore, another immunohistochemical investigation of CRC tumors revealed a strong correlation between mucinous histology and PD-L1 positivity [21, 74]. Overall, considering the frequency of MSI and hypermutation in MAC, these findings highlight the issue of whether Immune Checkpoint Inhibitor (ICI) therapy may constitute a viable treatment option for mucinous CRC. Further studies are needed to explore its efficacy [21].

In summary, resistance to chemotherapeutic drugs in mucinous CRC involves multiple mechanisms, including physical barriers, alterations in drug metabolism genes, and changes in the tumor immune microenvironment. Targeting these mechanisms through personalized treatment strategies, such as immune checkpoint inhibition, may improve outcomes for patients with mucinous CRC.

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3.6.6. Response to Chemo-Radiotherapy in mucinous rectal cancer

The response of mucinous colorectal cancer to neoadjuvant chemoradiotherapy (CRT) in locally advanced rectal cancer presents unique challenges compared to adenocarcinoma. Individuals with MAC tend to have a lower rate of tumor downsizing after CRT and are less likely to achieve a pathological complete response (pCR). This suggests a variation in susceptibility or innate resistance to CRT in mucinous cancer [66].

One possible explanation for the poor tumor response to CRT in MAC is the decreased vascular density, leading to less blood flow and a hypoxic state within the tumor. Additionally, the presence of a KRAS mutation, which is more common in MAC, is associated with an incomplete response to treatment in rectal cancer patients [66].

Despite the higher rate of positive circumferential resection margin (CRM) in MAC, this does not always correlate with a lower overall survival rate compared to non-mucinous adenocarcinoma. Positive CRM in MAC may indicate tumors with reduced cellular density and more tumor residues due to the presence of mucous near the tumor's perimeter. However, previous studies have shown that enhanced local control does not necessarily translate to longer survival, as distant metastases remain the primary determinant of longevity [66].

The challenges in assessing tumor response to CRT in MAC, particularly in distinguishing between tumors and inactive mucous lakes on MRI, highlight the need for improved imaging techniques and personalized treatment strategies for this subtype of colorectal cancer. Further research is necessary to elucidate the underlying mechanisms of resistance to CRT in MAC and to develop more effective therapeutic approaches tailored to the unique characteristics of mucinous tumors [66].

3.6.7. Targeted molecular therapy in mucinous colorectal cancer

Targeted therapy aims to target tumor cells while limiting harmful effects on normal tissue cells. At present, targeted therapy has become an integral part of the treatment approach for advanced or metastatic colorectal cancer (CRC), with cetuximab and bevacizumab being two commonly used drugs in this setting [35]. Cetuximab, which is anti-epidermal growth factor receptor antibody (anti-EGFR), is frequently used alongside with chemotherapy and bevacizumab is an anti-vascular endothelial growth factor monoclonal antibody (anti-VEGF). Nowadays, only few studies have explored the prognosis for cetuximab and

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bevacizumab treatment in mucinous versus non-mucinous colon cancer [19]. As it has already been noted, colorectal MAC is characterized by a higher prevalence of KRAS and BRAF mutations, and tumors are typically localized in the right colon. A study by De Roock et al. in metastatic CRC noticed that patients with KRAS mutations treated with cetuximab in combination with chemotherapy had lower median progression-free survival (PFS) (12 weeks vs. 24 weeks, $P < 0.0001$) and lower median overall survival (OS) (32 weeks vs. 50 weeks, $P < 0.0001$) compared to wild-type KRAS patients [75]. A more recent research revealed that anti-EGFR antibody therapy in conjunction with chemotherapy improved the prognosis for CRC patients with left-sided cancer but there was no apparent advantage for patients with right-sided malignancies [76].

However, in a study by Venook et al., patients with MAC in the right colon had a median OS of 24.5 months when treated with bevacizumab and chemotherapy, compared to 16.4 months for those treated with cetuximab [77]. Moreover, it is supported that FOLFOXIRI in combination with an anti-VEGF is an effective therapy strategy, regardless of RAS or BRAF mutation status [35]. In addition, another nationwide population study of 1235 patients with CRC and peritoneal metastases found that adding bevacizumab to chemotherapy resulted in a longer overall survival time than palliative treatment alone [78]. In 2015 was published a case report about a woman with locally advanced MAC in the transverse colon who received therapy for 4 months consisting of palliative metronomic capecitabine in combination with bevacizumab. She eventually responded well and had radical surgery and the treatment plan was altered from palliative to curative. This research supports the use of targeted molecular treatment for patients with MAC [79].

Considering the above, for patients with advanced mucinous colon cancer, anti-VEGF monoclonal antibody plus chemotherapy may be a better treatment option than anti-EGFR monoclonal antibody plus chemotherapy, especially if the tumors are found in the right colon and are RAS or BRAF mutated [35]. Bevacizumab, in particular, could serve as a first-line therapy for CRC patients and peritoneal dissemination, based on evidence from population studies and case reports [19]. Further investigation is needed to support this assumption.

Currently, other new medicines tailored for mucinous adenocarcinoma are being investigated. Mucus, a complex hydrogel coating epithelial surfaces, functions as a barrier between the underlying tissues and the external environment, influencing the medication penetration and activity. The mucous layer has pores ranging from 100 to 200 nm in size. Nanoparticles are the sole way to reach targeted tissues through these layers [19, 80]. Drug absorption relies on both solubility and lipophilicity. High solubility allows

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drugs to dissolve in body fluids, whereas high lipophilicity allows drugs to penetrate biological membranes. Combining poorly water-soluble lipophilic drugs with cyclodextrins is the ideal choice for creating water-soluble complexes with high permeability [81]. Although nanodrugs show potential in treating MAC, no clinical trials have been carried out to assess their response rate, safety and overall survival [66]. Another point of focus of current investigation is developing drugs targeting the actual mucin proteins or drugs that inhibit their synthesis, like MUC1-C inhibitor (GO-203), which hinders MUC1-C homo-oligomerization and an inhibitor of GCNT3 (core mucin-synthesizing enzyme), which serves a vital part in mucin glycan production, respectively [82, 83, 84]. However, further clinical trials are needed to assess the safety, efficacy, and overall survival benefits of these novel therapies in mucinous colorectal cancer patients.

3.6.8. Immunotherapy in Mucinous Colorectal Cancer

Immunotherapy with immune checkpoint inhibitors (ICIs) has emerged as a promising treatment approach for various types of cancer, including colorectal cancer [85]. Programmed cell Death protein 1(PD-1) with its ligand, PD-L1, limit T cell activation, reducing the immunological response to cancer cells. Inhibiting the PD-1 or PD-L1 pathway has profoundly enhanced outcomes in cancers such as non-small cell lung cancer, melanoma, and renal cell cancer [86]. These checkpoint molecules as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), and indoleamine 2,3-dioxygenase are highly expressed in tumors with mismatch repair deficiency MSI-high compared to microsatellite stable (MSS) tumors [73]. Moreover, especially in CRC, MSI-high CRC exhibits an increased tumor-infiltrating lymphocyte density and a pronounced Crohn's-like lymphoid reactivity compared to MSS CRC [87]. Regarding mucinous colorectal cancer in particular, the significantly elevated frequency of MSI-High could be linked to increased expression of PD-L1 in tumor cells and tumor-infiltrating immune cells in mucinous colorectal cancer as well [85].

It is noticeable that anti-PD-1 therapy has been verified to benefit oncologic patients with MSI-High tumors, and the same favorable results have been identified in CRC patients as well. Therefore, PD-1 inhibitor treatment is implied to be a promising treatment option for mucinous colorectal cancer [88].

Pembrolizumab (a humanized IgG4 monoclonal antibody that binds to PD-1) was the first medication to solely use biomarkers (MSI) to choose treatment alternatives based on overall response rates, without taking tumor types into account. In addition, further studies revealed that nivolumab (another PD-1 inhibitor) was beneficial in advanced MSI-High CRC in which cytotoxic medications were ineffective previously [89].

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As a result, starting in 2017, patients with MSI-High metastatic colorectal cancer got the formal recommendation of pembrolizumab or nivolumab as second- or third-line treatment in the National Comprehensive Cancer Network (NCCN) guidelines [90]. According to a study of Michael et al, nivolumab in combination with ipilimumab (CTLA-4 monoclonal antibody) should be considered an alternative of first-line therapy for patients with metastatic MSI-High CRC due to its more favorable response rate, long-term therapeutic advantages, and safety compared to anti-PD-1 monotherapy [91]. Moreover, the first results of phase 3 of the randomized controlled KEYNOTE-177 trial showed that patients with metastatic MSI-High CRC who received pembrolizumab as their first-line treatment had a considerably greater PFS (median, 16.5 vs 8.2 mo, P = 0.0002) and less treatment-related side effects (22% vs 66%) than those who received chemotherapy [92]. As a result, the US FDA authorized pembrolizumab as a first-line treatment for unresectable or metastatic MSI-High CRC in June 2020 [93]. Nevertheless, a subgroup analysis in the KEYNOTE-177 study suggested that pembrolizumab alone would not be beneficial for patients with metastatic MSI-High CRC who had mutations in the KRAS or NRAS [92]. It's uncertain if combining chemotherapy or anti-CTLA-4 with PD-1 inhibition can overcome this resistance [35]. In addition, the latest overall analysis of the study revealed no significant difference in the overall survival of the two groups but the treatment-related adverse effects remained less in the pembrolizumab group [94]. Unfortunately, specific data are limited for the subgroup of individuals with mucinous colorectal cancer in the literature. A study of O' Connell et al, including 557 cases of CRC tried to identify the immune checkpoint profile and the variables linked to the response to immune checkpoint inhibitors in MAC. Compared to non-mucinous CRC, MAC showed significantly increased expression of T cell immunoglobulin and mucin domain 3 (TIM-3), as well as programmed cell death protein 1 ligand (PD-L1). Microsatellite instability (MSI) and mucinous status were observed to be significant predictors of TIM-3 gene expression in a multiple regression model. Such results should stimulate further exploration into immune checkpoint activity in the mucinous tumor microenvironment to elucidate the possibility for immune checkpoint suppression specifically in mucinous CRC [95]. Currently, the use TIM-3 immune checkpoint inhibitor is on clinical trials and hopefully it will be included in the next wave of immune checkpoint inhibitors to be FDA approved for solid tumors [96].

The most recent NCCN guidelines for colon cancer on January 2024 recommend immunotherapy with immune checkpoint inhibitors in resectable locally advanced, clinical T4b MSI-High colon cancer as the primary therapy followed by surgery. The checkpoint inhibitor options include pembrolizumab or nivolumab with or without ipilimumab. It is also recommended in unresectable locally advanced MSI-High colon cancer in combination with chemotherapy in order to achieve conversion to resectability [97].

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Regarding rectal cancer, according to NCCN guidelines, for MSI-High cases that need neoadjuvant treatment or are locally unresectable, immunotherapy is the preferred treatment as neoadjuvant or definitive treatment. The checkpoint inhibitor options here include pembrolizumab, nivolumab or dorstalimab-gxly (PD-1 inhibitor) [98]. As for cases of metastatic MSI-High colorectal cancer, immunotherapy is still recommended as the first line therapy in eligible patients [97,98].

Combination therapy, including immune checkpoint inhibitors and targeted molecular therapy, holds promise for enhancing clinical outcomes in mucinous CRC [19]. Further research and clinical trials are needed to optimize treatment strategies for mucinous CRC and improve patient outcomes.

4. Conclusion

In conclusion, mucinous colorectal cancer presents a distinct clinical challenge due to its unique characteristics and prognosis. Its propensity for larger tumor size, advanced stage at diagnosis, and increased risk of peritoneal dissemination necessitate a tailored approach to both diagnosis and treatment. While advancements in diagnostic modalities and targeted therapies offer promise, further research is imperative to improve outcomes for patients with this subtype of colorectal cancer. By integrating multidisciplinary care, personalized treatment strategies, and ongoing surveillance, clinicians can strive to optimize patient outcomes and enhance overall survival in the management of mucinous colorectal cancer.

5. Abbreviations

MAC: Mucinous colorectal adenocarcinoma

MSI: Microsatellite Instability

CRC: colorectal cancer

FAP: familial adenomatous polyposis

HNPCC: hereditary nonpolyposis colorectal cancer

CIMP: CpG island methylator phenotype

APC: adenomatous polyposis coli gene

SCNA: somatic copy number alterations

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LOH: loss of heterozygosity

CMS: Consensus Molecular Subtypes

WHO: World Health Organization

VEGF: Vascular endothelial growth factor

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

FDG: fluorodeoxyglucose

CRM: circumferential resection margin

TME: total mesorectal excision

ypCRM: post-neoadjuvant circumferential resection margin

TNM: Tumor, Node, Metastasis

CME: complete mesocolic excision

JSCCR: Japanese Society for Cancer of the Colon and Rectum

ASCRS: American Society of Colon and Rectal Surgeons

M-CLM: mucinous colon cancer and liver metastases

A-CLM: adenocarcinoma of the colon and liver metastases

CRS: Cytoreductive Surgery

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

TYMS: thymidyl late synthase

GSTP1: glutathione S-transferase p1

TYMP: Thymidine phosphorylase

CRT: chemoradiotherapy

pCR: pathological complete response

anti-EGFR: anti-epidermal growth factor receptor antibody

anti-VEGF: anti-vascular endothelial growth factor monoclonal antibody

PFS: progression-free survival

OS: overall survival

FOLFOXIRI: Folinic acid, fluorouracil, oxaliplatin and irinotecan

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ICIs: immune checkpoint inhibitors

PD-1: Programmed cell Death protein 1

PD-L1: Programmed cell Death protein 1 ligand

CTLA-4: cytotoxic T-lymphocyte-associated protein 4

LAG-3: lymphocyte activation gene 3

MSS: microsatellite stable

NCCN: National Comprehensive Cancer Network

US FDA: United States Food and Drug Administration

TIM-3: T cell immunoglobulin and mucin domain 3

6. References

1. Sung H, Ferlay J, Siegel RL, 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(3):209-249. doi:10.3322/caac.21660
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691. doi:10.1136/gutjnl-2015-310912
3. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol*. 2019;16(12):713-732. doi:10.1038/s41575-019-0189-8
4. Nguyen LH, Goel A, Chung DC. Pathways of Colorectal Carcinogenesis. *Gastroenterology*. 2020;158(2):291-302. doi:10.1053/j.gastro.2019.08.059
5. De Palma FDE, D'Argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The Molecular Hallmarks of the Serrated Pathway in Colorectal Cancer. *Cancers (Basel)*. 2019;11(7):1017. Published 2019 Jul 20. doi:10.3390/cancers11071017
6. Rejali L, Seifollahi Asl R, Sanjabi F, et al. Principles of Molecular Utility for CMS Classification in Colorectal Cancer Management. *Cancers (Basel)*. 2023;15(10):2746. Published 2023 May 13. doi:10.3390/cancers15102746

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

7. Toyota M, Ahuja N, Ohe-Toyota M, Herman JG, Baylin SB, Issa JP. CpG island methylator phenotype in colorectal cancer. *Proc Natl Acad Sci U S A*. 1999;96(15):8681-8686. doi:10.1073/pnas.96.15.8681
8. Roseweir AK, McMillan DC, Horgan PG, Edwards J. Colorectal cancer subtypes: Translation to routine clinical pathology. *Cancer Treat Rev*. 2017;57:1-7. doi:10.1016/j.ctrv.2017.04.006
9. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21(11):1350-1356. doi:10.1038/nm.3967
10. Missiaglia E, Jacobs B, D'Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features [published correction appears in Ann Oncol. 2015 Feb;26(2):445]. *Ann Oncol*. 2014;25(10):1995-2001. doi:10.1093/annonc/mdu275
11. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487(7407):330-337. Published 2012 Jul 18. doi:10.1038/nature11252
12. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol*. 2012;3(3):153-173. doi:10.3978/j.issn.2078-6891.2012.030
13. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. *J Clin Pathol*. 2012;65(5):381-388. doi:10.1136/jclinpath-2011-200340
14. Ott C, Gerken M, Hirsch D, et al. Advanced Mucinous Colorectal Cancer: Epidemiology, Prognosis and Efficacy of Chemotherapeutic Treatment. *Digestion*. 2018;98(3):143-152. doi:10.1159/000487710
15. Catalano V, Loupakis F, Graziano F, et al. Prognosis of mucinous histology for patients with radically resected stage II and III colon cancer. *Ann Oncol*. 2012;23(1):135-141. doi:10.1093/annonc/mdr062
16. Warschkow R, Tarantino I, Huttner FJ, et al. Predictive value of mucinous histology in colon cancer: a population-based, propensity score matched analysis. *Br J Cancer*. 2016;114(9):1027-1032. doi:10.1038/bjc.2016.57
17. Numata M, Shiozawa M, Watanabe T, et al. The clinicopathological features of colorectal mucinous adenocarcinoma and a therapeutic strategy for the disease. *World J Surg Oncol*. 2012;10:109. Published 2012 Jun 15. doi:10.1186/1477-7819-10-109
18. Hugen N, Verhoeven RH, Radema SA, et al. Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma. *Ann Oncol*. 2013;24(11):2819-2824. doi:10.1093/annonc/mdt378

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

19. Luo C, Cen S, Ding G, Wu W. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options. *Cancer Commun (Lond)*. 2019;39(1):13. Published 2019 Mar 29. doi:10.1186/s40880-019-0361-0
20. Reynolds IS, Furney SJ, Kay EW, McNamara DA, Prehn JHM, Burke JP. Meta-analysis of the molecular associations of mucinous colorectal cancer. *Br J Surg*. 2019;106(6):682-691. doi:10.1002/bjs.11142
21. O'Connell E, Reynolds IS, McNamara DA, Burke JP, Prehn JHM. Resistance to Cell Death in Mucinous Colorectal Cancer-A Review. *Cancers (Basel)*. 2021;13(6):1389. Published 2021 Mar 19. doi:10.3390/cancers13061389
22. Leystra AA, Deming DA, Zahm CD, et al. Mice expressing activated PI3K rapidly develop advanced colon cancer. *Cancer Res*. 2012;72(12):2931-2936. doi:10.1158/0008-5472.CAN-11-4097
23. Hugen N, van Beek JJ, de Wilt JH, Nagtegaal ID. Insight into mucinous colorectal carcinoma: clues from etiology. *Ann Surg Oncol*. 2014;21(9):2963-2970. doi:10.1245/s10434-014-3706-6
24. Kang J, Lee HW, Kim IK, Kim NK, Sohn SK, Lee KY. Clinical implications of microsatellite instability in T1 colorectal cancer. *Yonsei Med J*. 2015;56(1):175-181. doi:10.3349/ymj.2015.56.1.175
25. Andrici J, Farzin M, Sioson L, et al. Mismatch repair deficiency as a prognostic factor in mucinous colorectal cancer. *Mod Pathol*. 2016;29(3):266-274. doi:10.1038/modpathol.2015.159
26. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. *Curr Treat Options Oncol*. 2015;16(7):30. doi:10.1007/s11864-015-0348-2
27. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology*. 2013;62(3):367-386. doi:10.1111/his.12055
28. Rosty C, Young JP, Walsh MD, et al. Colorectal carcinomas with KRAS mutation are associated with distinctive morphological and molecular features. *Mod Pathol*. 2013;26(6):825-834. doi:10.1038/modpathol.2012.240
29. Lin JK, Chang SC, Wang HS, et al. Distinctive clinicopathological features of Ki-ras mutated colorectal cancers. *J Surg Oncol*. 2006;94(3):234-241. doi:10.1002/jso.20438
30. Pai RK, Jayachandran P, Koong AC, et al. BRAF-mutated, microsatellite-stable adenocarcinoma of the proximal colon: an aggressive adenocarcinoma with poor survival, mucinous differentiation,

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

and adverse morphologic features. *Am J Surg Pathol*. 2012;36(5):744-752. doi:10.1097/PAS.0b013e31824430d7

31. Yokota T, Ura T, Shibata N, et al. BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. *Br J Cancer*. 2011;104(5):856-862. doi:10.1038/bjc.2011.19
32. Thiel A, Ristimäki A. Toward a Molecular Classification of Colorectal Cancer: The Role of BRAF. *Front Oncol*. 2013;3:281. Published 2013 Nov 15. doi:10.3389/fonc.2013.00281
33. Capper D, Voigt A, Bozukova G, et al. BRAF V600E-specific immunohistochemistry for the exclusion of Lynch syndrome in MSI-H colorectal cancer. *Int J Cancer*. 2013;133(7):1624-1630. doi:10.1002/ijc.28183
34. Okudaira K, Kakar S, Cun L, et al. MUC2 gene promoter methylation in mucinous and non-mucinous colorectal cancer tissues. *Int J Oncol*. 2010;36(4):765-775. doi:10.3892/ijo_00000552
35. Huang A, Yang Y, Shi JY, et al. Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer. *World J Gastrointest Surg*. 2021;13(12):1567-1583. doi:10.4240/wjgs.v13.i12.1567
36. Li ZH, You DY, Gao DP, et al. Role of CT scan in differentiating the type of colorectal cancer. *Onco Targets Ther*. 2017;10:2297-2303. Published 2017 Apr 26. doi:10.2147/OTT.S131008
37. Horvat N, Hope TA, Pickhardt PJ, Petkovska I. Mucinous rectal cancer: concepts and imaging challenges. *Abdom Radiol (NY)*. 2019;44(11):3569-3580. doi:10.1007/s00261-019-02019-x
38. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: correlation of FDG uptake with histopathologic features. *AJR Am J Roentgenol*. 2000;174(4):1005-1008. doi:10.2214/ajr.174.4.1741005
39. Dos Anjos DA, Habr-Gama A, Vailati BB, et al. (18)F-FDG uptake by rectal cancer is similar in mucinous and nonmucinous histological subtypes. *Ann Nucl Med*. 2016;30(8):513-517. doi:10.1007/s12149-016-1089-4
40. Kim MJ, Park JS, Park SI, et al. Accuracy in differentiation of mucinous and nonmucinous rectal carcinoma on MR imaging. *J Comput Assist Tomogr*. 2003;27(1):48-55. doi:10.1097/00004728-200301000-00010
41. Oberholzer K, Menig M, Kreft A, et al. Rectal cancer: mucinous carcinoma on magnetic resonance imaging indicates poor response to neoadjuvant chemoradiation. *Int J Radiat Oncol Biol Phys*. 2012;82(2):842-848. doi:10.1016/j.ijrobp.2010.08.057

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

42. Gosens MJ, Klaassen RA, Tan-Go I, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. *Clin Cancer Res*. 2007;13(22 Pt 1):6617-6623. doi:10.1158/1078-0432.CCR-07-1197
43. Mawdsley S, Glynne-Jones R, Grainger J, et al. Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for 3-year disease-free survival?. *Int J Radiat Oncol Biol Phys*. 2005;63(3):745-752. doi:10.1016/j.ijrobp.2005.03.003
44. Huang Q, Zou MH, Jiang Y, et al. Outcomes of Laparoscopic Surgery for Mucinous Colorectal Adenocarcinoma. *J Laparoendosc Adv Surg Tech A*. 2021;31(6):638-647. doi:10.1089/lap.2020.0588
45. Heald RJ. A new approach to rectal cancer. *Br J Hosp Med*. 1979;22(3):277-281.
46. Votava J, Kachlik D, Hoch J. Total mesorectal excision - 40 years of standard of rectal cancer surgery. *Acta Chir Belg*. 2020;120(4):286-290. doi:10.1080/00015458.2020.1745529
47. Ishiguro M, Higashi T, Watanabe T, Sugihara K; Japanese Society for Cancer of the Colon and Rectum Guideline Committee. Changes in colorectal cancer care in japan before and after guideline publication: a nationwide survey about D3 lymph node dissection and adjuvant chemotherapy. *J Am Coll Surg*. 2014;218(5):969-977.e1. doi:10.1016/j.jamcollsurg.2013.12.046
48. Vogel JD, Felder SI, Bhama AR, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Dis Colon Rectum*. 2022;65(2):148-177. doi:10.1097/DCR.0000000000002323
49. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2020;25(1):1-42. doi:10.1007/s10147-019-01485-z
50. Gupta A, Garabetian C, Cologne K, Duldulao MP. Complete mesocolic excision and extended lymphadenectomy: Where should we stand?. *J Surg Oncol*. 2024;129(2):338-348. doi:10.1002/jso.27475
51. Vogelsang RP, Klein MF, Gögenur I. Risk Factors for Compromised Surgical Resection: A Nationwide Propensity Score-Matched Study on Laparoscopic and Open Resection for Colonic Cancer. *Dis Colon Rectum*. 2019;62(4):438-446. doi:10.1097/DCR.0000000000001304
52. van Gestel YR, Thomassen I, Lemmens VE, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol*. 2014;40(8):963-969. doi:10.1016/j.ejso.2013.10.001

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

53. Bagante F, Spolverato G, Beal E, et al. Impact of histological subtype on the prognosis of patients undergoing surgery for colon cancer. *J Surg Oncol*. 2018;117(7):1355-1363. doi:10.1002/jso.25044
54. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422. doi:10.1093/annonc/mdw235
55. Huang J, Chen G, Liu H, et al. Surgery improves the prognosis of colon mucinous adenocarcinoma with liver metastases: a SEER-based study. *BMC Cancer*. 2020;20(1):908. Published 2020 Sep 23. doi:10.1186/s12885-020-07400-4
56. Hugen N, van de Velde CJH, de Wilt JHW, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. *Ann Oncol*. 2014;25(3):651-657. doi:10.1093/annonc/mdt591
57. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Med*. 2020;9(1):361-373. doi:10.1002/cam4.2673
58. Govaert KM, Jongen JMJ, Kranenburg O, Borel Rinkes IHM. Surgery-induced tumor growth in (metastatic) colorectal cancer. *Surg Oncol*. 2017;26(4):535-543. doi:10.1016/j.suronc.2017.10.004
59. Fonseca GM, Herman P, Faraj SF, et al. Pathological factors and prognosis of resected liver metastases of colorectal carcinoma: implications and proposal for a pathological reporting protocol. *Histopathology*. 2018;72(3):377-390. doi:10.1111/his.13378
60. Nitsche U, Zimmermann A, Späth C, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. *Ann Surg*. 2013;258(5):775-783. doi:10.1097/SLA.0b013e3182a69f7e
61. Sugarbaker PH. Patient selection and treatment of peritoneal carcinomatosis from colorectal and appendiceal cancer. *World J Surg*. 1995;19(2):235-240. doi:10.1007/BF00308632
62. Song W, Wu SJ, He YL, et al. Clinicopathologic features and survival of patients with colorectal mucinous, signet-ring cell or non-mucinous adenocarcinoma: experience at an institution in southern China. *Chin Med J (Engl)*. 2009;122(13):1486-1491.
63. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):256-266. doi:10.1016/S1470-2045(20)30599-4

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

64. Klempner SJ, Ryan DP. HIPEC for colorectal peritoneal metastases. *Lancet Oncol*. 2021;22(2):162-164. doi:10.1016/S1470-2045(20)30693-8
65. Herold Z, Acs M, Szasz AM, et al. Patients with Metachronous Peritoneal Metastatic Mucinous Colorectal Adenocarcinoma Benefit More from Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) than Their Synchronous Counterparts. *Cancers (Basel)*. 2022;14(16):3978. Published 2022 Aug 17. doi:10.3390/cancers14163978
66. 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):361-369. doi:10.1038/nrclinonc.2015.140
67. Reynolds IS, O'Connell E, Fichtner M, et al. Mucinous adenocarcinoma is a pharmacogenomically distinct subtype of colorectal cancer. *Pharmacogenomics J*. 2020;20(3):524-532. doi:10.1038/s41397-019-0137-6
68. Glasgow SC, Yu J, Carvalho LP, Shannon WD, Fleshman JW, McLeod HL. Unfavourable expression of pharmacologic markers in mucinous colorectal cancer. *Br J Cancer*. 2005;92(2):259-264. doi:10.1038/sj.bjc.6602330
69. Johansson ME, Hansson GC. Immunological aspects of intestinal mucus and mucins. *Nat Rev Immunol*. 2016;16(10):639-649. doi:10.1038/nri.2016.88
70. Tozawa E, Ajioka Y, Watanabe H, et al. Mucin expression, p53 overexpression, and peritumoral lymphocytic infiltration of advanced colorectal carcinoma with mucus component: is mucinous carcinoma a distinct histological entity?. *Pathol Res Pract*. 2007;203(8):567-574. doi:10.1016/j.prp.2007.04.013
71. Nazemalhosseini-Mojarad E, Mohammadpour S, Torshizi Esafahani A, et al. Intratumoral infiltrating lymphocytes correlate with improved survival in colorectal cancer patients: Independent of oncogenetic features. *J Cell Physiol*. 2019;234(4):4768-4777. doi:10.1002/jcp.27273
72. Zhao Y, Ge X, Xu X, Yu S, Wang J, Sun L. Prognostic value and clinicopathological roles of phenotypes of tumour-associated macrophages in colorectal cancer. *J Cancer Res Clin Oncol*. 2019;145(12):3005-3019. doi:10.1007/s00432-019-03041-8
73. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. 2015;372(26):2509-2520. doi:10.1056/NEJMoa1500596
74. Jung DH, Park HJ, Jang HH, Kim SH, Jung Y, Lee WS. Clinical Impact of PD-L1 Expression for Survival in Curatively Resected Colon Cancer. *Cancer Invest*. 2020;38(7):406-414. doi:10.1080/07357907.2020.1793349

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04/09/2026 19:16:39 EEST - 216.73.216.250

75. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol*. 2010;11(8):753-762. doi:10.1016/S1470-2045(10)70130-3
76. Arnold D, Lueza B, Douillard JY, 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):1713-1729. doi:10.1093/annonc/mdx175
77. Alan P. Venook et al.Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance).. *JCO* **34**, 3504-3504(2016). doi:10.1200/JCO.2016.34.15_suppl.3504
78. 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 Colorectal Cancer*. 2016;15(2):e41-e46. doi:10.1016/j.clcc.2015.12.006
79. Vernmark K, Albertsson M, Björnsson B, 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. Published 2015 Nov 10. doi:10.1186/s12885-015-1908-3
80. 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):229-244. doi:10.4155/tde-2015-0002
81. Loftsson T. Drug permeation through biomembranes: cyclodextrins and the unstirred water layer. *Pharmazie*. 2012;67(5):363-370.
82. Morimoto Y, Yamashita N, Hirose H, et al. MUC1-C is necessary for SHP2 activation and BRAF inhibitor resistance in BRAF(V600E) mutant colorectal cancer. *Cancer Lett*. 2023;559:216116. doi:10.1016/j.canlet.2023.216116
83. Ahmad R, Alam M, Hasegawa M, et al. Targeting MUC1-C inhibits the AKT-S6K1-elF4A pathway regulating TIGAR translation in colorectal cancer. *Mol Cancer*. 2017;16(1):33. Published 2017 Feb 2. doi:10.1186/s12943-017-0608-9
84. Rao CV, Janakiram NB, Mohammed A. Molecular Pathways: Mucins and Drug Delivery in Cancer. *Clin Cancer Res*. 2017;23(6):1373-1378. doi:10.1158/1078-0432.CCR-16-0862

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

85. Kim JH, Park HE, Cho NY, Lee HS, Kang GH. Characterisation of PD-L1-positive subsets of microsatellite-unstable colorectal cancers. *Br J Cancer*. 2016;115(4):490-496. doi:10.1038/bjc.2016.211
86. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454. doi:10.1056/NEJMoa1200690
87. Rozek LS, Schmit SL, Greenson JK, et al. Tumor-Infiltrating Lymphocytes, Crohn's-Like Lymphoid Reaction, and Survival From Colorectal Cancer. *J Natl Cancer Inst*. 2016;108(8):djw027. Published 2016 May 12. doi:10.1093/jnci/djw027
88. 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):16-18. doi:10.1158/2159-8290.CD-14-1397
89. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413. doi:10.1126/science.aan6733
90. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15(3):370-398. doi:10.6004/jnccn.2017.0036
91. 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):773-779. doi:10.1200/JCO.2017.76.9901
92. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med*. 2020;383(23):2207-2218. doi:10.1056/NEJMoa2017699
93. Smith SM, Wachter K, Burris HA 3rd, et al. Clinical Cancer Advances 2021: ASCO's Report on Progress Against Cancer. *J Clin Oncol*. 2021;39(10):1165-1184. doi:10.1200/JCO.20.03420
94. Kai-Keen Shiu et al.KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer.. *JCO* **39**, 6-6(2021).doi:10.1200/JCO.2021.39.3_suppl.6
95. O'Connell E, Salvucci M, Reynolds IS, McNamara DA, Burke JP, Prehn JHM. Mucinous Colorectal Cancer is Associated With Expression of the TIM-3 Immune Checkpoint Independently of Microsatellite Instability (MSI) Status. *Ann Surg Oncol*. 2021;28(12):7999-8006. doi:10.1245/s10434-021-09873-4

Institutional Repository - Library & Information Centre - University of Thessaly
04/09/2026 19:16:39 EEST - 216.73.216.250

96. Cai L, Li Y, Tan J, Xu L, Li Y. Targeting LAG-3, TIM-3, and TIGIT for cancer immunotherapy [published correction appears in J Hematol Oncol. 2023 Sep 29;16(1):105]. *J Hematol Oncol*. 2023;16(1):101. Published 2023 Sep 5. doi:10.1186/s13045-023-01499-1
97. National Comprehensive Cancer Network. Colon Cancer (Version 3.2024). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 24, 2024
98. National Comprehensive Cancer Network. Rectal Cancer (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed April 30, 2024

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04/09/2026 19:16:39 EEST - 216.73.216.250