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## Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer

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### Abstract

Mucinous adenocarcinoma (MAC) is a unique clinicopathological subtype of colorectal cancer, which is characterized by extracellular mucinous components that comprise at least 50% of the tumor tissue. The clinical characteristics, molecular features, response to chemo-/radiotherapy, and prognosis of MAC are different from that of non-MAC (NMAC). MAC is more common in the proximal colon, with larger volume, higher T-stage, a higher proportion of positive lymph nodes, poorer tumor differentiation, and a higher proportion of peritoneal implants compared to NMAC. Although biopsy is the main diagnostic method for MAC, magnetic resonance imaging is superior in accuracy, especially for rectal carcinoma. The aberrant expression of mucins, including MUC1, MUC2 and MUC5AC, is a notable feature of MAC, which may be related to tumor invasion, metastasis, inhibition of apoptosis, and chemo-/radiotherapy resistance. The genetic origin of MAC is mainly related to *BRAF* mutation, microsatellite instability, and the CpG island methylator phenotype pathway. In addition, the poor prognosis of rectal MAC has been confirmed by various studies, and that of colonic MAC is still controversial. In this review, we summarize the epidemiology, clinicopathological characteristics, molecular features, methods of diagnosis, and treatments of MAC in order to provide references for further fundamental and clinical research.

**Key Words:** Mucinous adenocarcinoma; Colorectal cancer; Mucin; Microsatellite

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**Core tip:** Colorectal mucinous adenocarcinoma (MAC) is a unique clinicopathological subtype in colorectal cancer. MAC exhibits a higher frequency of microsatellite instability, higher CpG island methylator phenotype of high degree, higher frequency of *BRAF* and *KRAS* gene mutations, and lower frequency of *TP53* mutations. One of the most important features of MAC is the aberrant expression of a large number of mucins, including MUC1, MUC2 and MUC5AC. We discuss the epidemiology, clinicopathological characteristics, molecular features, methods of diagnosis, and treatments of MAC in order to provide references for further fundamental and clinical research.

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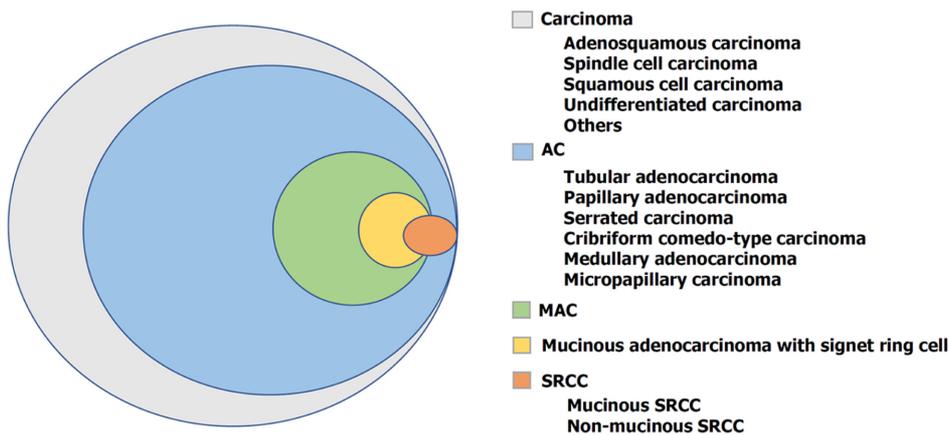
## INTRODUCTION

Colorectal cancer (CRC) has caused a great burden on global health. The World Health Organization (WHO) estimated > 1.9 million new CRC cases and 935 000 CRC-related deaths occurred in 2020, with 10% (third) and 9.4% (second) incidence and mortality rates, respectively, among all cancer types[1]. According to the WHO classification of tumors of the digestive system, the histological subtypes of CRC include adenocarcinoma, adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma (Figure 1). Adenocarcinoma originating from epithelial cells of the colorectal mucosa accounts for more than 90% of CRC cases. Mucinous adenocarcinoma (MAC) is a unique subtype of adenocarcinoma characterized by more than 50% of the tumor tissue being extracellular mucinous components. Malignant epithelial cells float in the mucus, forming alveolar, row-like, or single-scattered cells. Tumors with a significant mucinous component (10-50%) are usually referred to as adenocarcinoma with mucinous features or mucinous differentiation[2,3]. Although the highly malignant biological behavior of MAC is well known, its related mechanisms have not been extensively studied.

Compared to non-MAC (NMAC), the clinicopathological characteristics, molecular features, response to chemo-/radiotherapy, and prognosis of MAC are evidently different. MAC are divided into two types based on the degree of histological structural differences: One type is the low-grade MAC, which originates from well-differentiated to moderately differentiated adenocarcinoma and papillary carcinoma, whereas the other type is the high-grade MAC, originated from poorly differentiated adenocarcinoma and signet ring cell carcinoma (SRCC)[4]. Currently, the prognosis of MAC remains controversial. Previous studies have suggested that colorectal MAC is associated with poor prognosis[5-8], while other studies reported no significant difference in prognosis between MAC and NMAC[9,10]. However, the poor prognosis of rectal MAC has been confirmed in most studies[11-13]. The clinicopathological characteristics of MAC suggest that it is a unique subtype of CRC.

## EPIDEMIOLOGICAL AND CLINICOPATHOLOGICAL CHARACTERISTICS OF COLORECTAL MAC

Various studies have demonstrated regional differences in the occurrence of MAC in CRC. The occurrence of MAC in CRC was 6.9%[14], 8.9%[15], 8.17%[16] in China, 3.82%[17], 2.8%[18] in Japan, 11.6%[19], 10%[5] and 11%[20] in the USA, which ranged from 3.9% in Asia to 10%-13.6% in Europe and North America[21]. A large national



**Figure 1** World Health Organization histological classification of colorectal carcinoma. AC: Adenocarcinoma; MAC: Mucinous adenocarcinoma; SRCC: Signet ring cell carcinoma.

cancer database study in the USA demonstrated that the distribution of histological subtypes of CRC among Caucasians, African Americans, and other races were similar [22]. However, another study reported that the occurrence of MAC in Chinese Americans with CRC (7.5%) was lower than that in Caucasians (9.3%) and African Americans (9.4%)[23]. This might be due to genetic differences between races as well as other factors (such as lifestyle and dietary habits). Studies on American[6] and German patients[24] found that MAC occurred in a higher proportion of women (MAC *vs* NMAC, 52.1% *vs* 48.6%, 47% *vs* 41%, respectively). In addition, a German study observed no difference in the age of patients with MAC and NMAC, whereas an American study observed that the proportion of MAC in patients aged > 65 years was higher. However, studies on Chinese patients reported no statistical difference in gender between patients with MAC and NMAC, and that MAC was more common in patients aged < 50 years[25].

Compared with that in NMAC, in MAC, the proportion of tumors occurring in the right hemicolon was higher (MAC *vs* NMAC, 35.0% *vs* 18.9% in China[25], 65.3% *vs* 46.2% in the USA[6], 51.0% *vs* 28.0% in Germany[24]), while the proportion of tumors in the rectum was lower (MAC *vs* NMAC, 41.0% *vs* 50.7% in China, 9.9% *vs* 17.7% in the USA, 27.0% *vs* 40.0% in Germany) in MAC. MAC was diagnosed with larger tumors, higher T stage, higher proportion of lymph node infiltration and peritoneal implantation, and poorer tumor differentiation compared to NMAC (Table 1)[6,24-27].

## MOLECULAR CHARACTERISTICS OF COLORECTAL MAC

MAC exhibited a higher frequency of microsatellite instability (MSI) and *BRAF* and *KRAS* gene mutations, higher CpG island methylator phenotype of high degree (CIMP-H), and lower frequency of *TP53* mutations[28]. Gene expression analysis illustrated that compared to NMAC, 317 genes were differentially regulated in MAC, of which 182 were upregulated and 135 were downregulated. These altered genes were primarily involved in O-glycan biosynthesis, keratin sulfate metabolism, lacto-series glycosphingolipid metabolism, histidine-glutamate-glutamine and proline metabolism, p38-MAPK pathway, coenzyme A biosynthesis, and 14-3-3 protein in cell cycle regulation[26]. Among them, O-glycan biosynthesis is associated with mucins synthesis. One of the most important features of MAC, the aberrant expression of several mucins, is associated with O-polysaccharide biosynthesis, including MUC1, MUC2, and MUC5AC[29].

### Expression of mucins in MAC

Mucins are a class of high-molecular-weight epithelial glycoproteins with a high content of clustered oligosaccharides O-glycosidically linked to tandem repeat peptides rich in threonine, serine and proline[29]. They are differentially expressed by specialized epithelial cells on the mucosal surface in a specific way for organs and cells [30]. Mucins are classified as membrane-associated and secreted mucins. Secreted mucins are either gel-forming or non-gel-forming subtypes[31]. Under normal circumstances, mucins form a mucus barrier that protects the epithelial cells. In the process of

**Table 1 Clinicopathological characteristics of patients with mucinous adenocarcinoma or non-mucinous adenocarcinoma in China, USA and Germany[6,24,25]**

	China			USA			Germany		
	MAC (%)	NMAC (%)	P	MAC (%)	NMAC (%)	P	MAC (%)	NMAC (%)	P
Age(yr)	21.4% (< 50)	11.3% (< 50)	0.005	62.6% (> 65)	56.3% (> 65)	< 0.001	67 (25-88)	65 (15-96)	0.037
Gender			0.603			< 0.001			0.034
Male	58.1	55.4		47.9	51.4		52.8	58.5	
Female	41.9	44.6		52.1	48.6		47.2	41.5	
Tumor location			< 0.001			< 0.001			< 0.001
Right hemicolon	35.0	18.9		65.3	46.2		51.5	27.5	
Left hemicolon	23.9	30.4		24.8	36.2		18.9	29.8	
Rectum	41.0	50.7		9.9	17.6		27.5	40.1	
Tumor size (cm)			< 0.001			< 0.001			-
≤ 5	34.2	54.2		48.93	68.34		-	-	
> 5	65.8	45.8		51.07	31.66		-	-	
Primary tumor (T)			0.001			< 0.001			< 0.001
T1, T2	28.2	44.5		13.8	26.5		13.3	30.5	
T3, T4	71.8	55.4		86.2	73.5		86.7	69.5	
Regional lymph nodes (N)			< 0.001			< 0.001			0.018
N0	35.9	55.0		52.5	57.0		49.1	55.6	
N1, N2	64.0	45.0		47.5	43.0		50.9	44.4	
Distant metastasis (M)			0.001			0.004			< 0.001
M0	56.4	72.4		84.7	85.8		75.5	78.5	
M1	43.6	27.6		15.3	14.2		24.5	21.5	
Stage			0.001			< 0.001			< 0.001
I, II	28.2	44.5		21.5	31.2		44.8	52.0	
III, IV	71.8	55.5		78.5	68.8		55.2	48.0	
Histological grading			< 0.001			< 0.001			< 0.001
G1, G2	82.9	89.8		76.4	80.1		55.2	69.6	
G3, G4	17.1	10.1		23.6	19.9		44.8	30.4	

P value of the  $\chi^2$  test was used to compare the NMAC and MAC groups. MAC: mucinous adenocarcinoma; NMAC: nonmucinous adenocarcinoma.

tumorigenesis, aberrant expression of specific mucins may be related to tumor invasion, metastasis, apoptosis inhibition, and chemoradiotherapy resistance[32]. MUC1, MUC2 and MUC5AC are aberrantly expressed in colorectal MAC. MUC1 is a membrane-associated mucin, while MUC2 and MUC5AC are secreted gel-forming mucins[31].

MUC1 is expressed in almost all glandular epithelial cell membranes, making MUC1 overexpression one of the most common changes in cancers. During pathogen infection, upregulation of MUC1 expression in the mucosal barrier suppresses pathogen-mediated inflammation[33]. However, MUC1 expression is induced by inflammatory cytokines [tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , and interleukin (IL)-6], and abnormal activation of MUC1 may lead to chronic inflammation and cancers in the absence of IL-10 and corresponding anti-inflammatory responses[34]. MUC1 C-terminal transmembrane subunit (MUC1-C) can activate both the inhibitor of nuclear factor- $\kappa$ B (NF- $\kappa$ B) kinase- $\beta$  (IKK $\beta$ ) and the NF- $\kappa$ B family member RELA, while the activation of the IKK $\beta$ -NF- $\kappa$ B pathway is a likely mediator of inflammation-induced cancer progression[35,36]. Meanwhile, MUC1 can inhibit tumor cell apoptosis *via* the

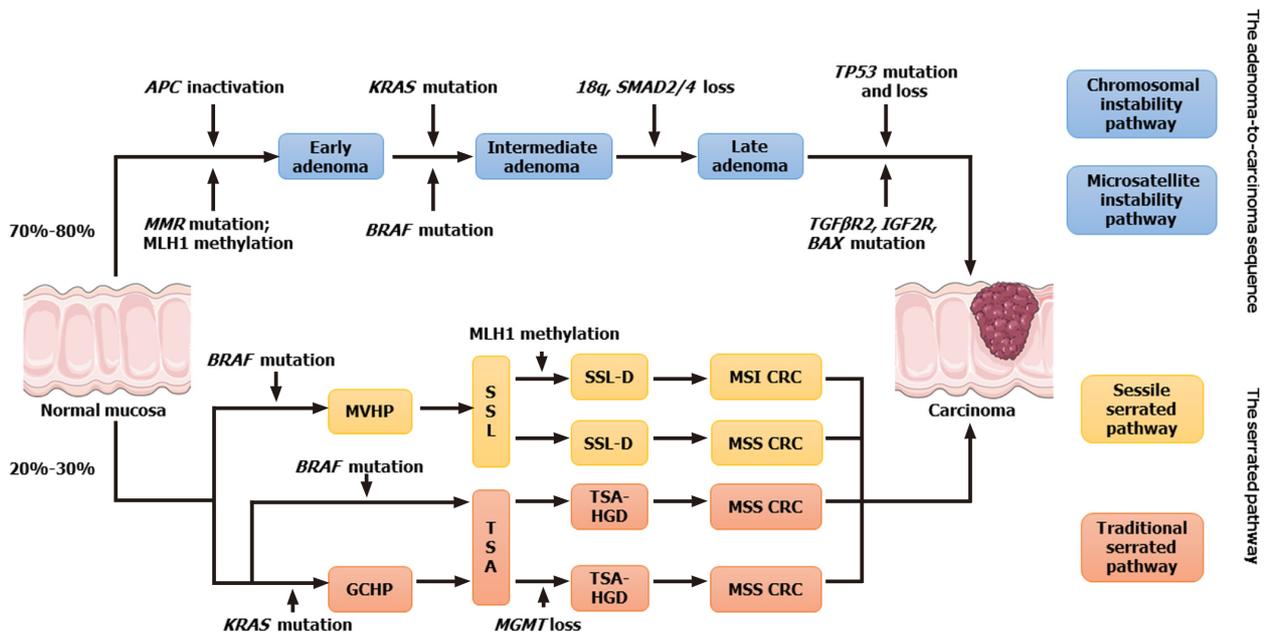
abnormal activation of NF- $\kappa$ B and Wnt/ $\beta$ -catenin signaling pathways, inhibition of the JNK1 signaling pathway, and formation of a physical barrier to prevent chemotherapeutic drugs from reaching tumor cells[32]. The resistance of MAC to chemoradiotherapy may be reversed by reducing the production of mucins or inhibiting their functions. Studies have been targeting MUC1 as a cancer vaccine for CRC, which reduces tumor burden and induces tumor regression in mouse models[37,38]. However, their application to patients with MAC requires further research.

MUC2 primarily exists in goblet cells of the colorectum, especially in the proximal colon, and is an important component of normal intestinal mucus, which acts as a physical barrier thereby limiting the damage to the epithelium by pathogens and weaken the activation of natural and acquired immune responses[39]. Feagins *et al* observed that the degree of ulcerative colitis was associated with reduction in MUC2 levels, while chronic inflammation associated with inflammatory bowel disease increased the risk of colon cancer[40]. MUC2 is strongly expressed in normal colon tissues (mean composite score  $\pm$  standard error,  $12 \pm 0$ ), and decreases sequentially in inflammation, hyperplastic polyps, and adenomas ( $11.4 \pm 0.4$ ,  $9.7 \pm 1.1$ ,  $7.4 \pm 0.6$ , respectively), while in adenocarcinoma, the expression of MUC2 is significantly decreased ( $3.8 \pm 0.9$ )[41]. Low levels of MUC2 are associated with poor overall survival (OS) [hazard ratio (HR) = 1.67, 95% confidence interval (CI): 1.43-1.94,  $P < 0.00001$ ][42], which suggests that MUC2 can act as a tumor suppressor. However, compared to NMAC, MAC with no better prognosis overexpresses MUC2, which is inconsistent with the observation that MUC2 acts as a tumor suppressor. Gratchev *et al*[43] found that the strong expression of MUC2 in normal human goblet cells and human colorectal MAC tissues was related to  $\sim 50\%$  of the average degree of methylation at the CpG site of each MUC2 promoter. MUC2 promoters in normal columnar cells and NMAC tissues that do not express MUC2 are methylated to nearly 100%. In this regard, MUC2 expression in carcinomas might reflect the origin of these tumors from cells that normally express MUC2, rather than a role for this mucin in the malignant process itself[34].

Another component of the mucus secreted by colorectal MAC is MUC5AC, which is usually secreted by tracheobronchial goblet cells, gastric epithelial cells, conjunctiva, and lacrimal gland cells, but is not expressed in the normal colonic mucosa[31,44]. Studies have shown that during adenoma-adenocarcinoma progression, the expression of MUC5AC is upregulated[41], which may be associated with transcription factors such as Smad-4, SP-1[45], GATA-6 and HNF-4 $\alpha$ [46], sex determining region Y-box 2[47], and trefoil factor 3[48]. Although MUC5AC expression is upregulated in MAC, the expression of MUC5AC in low-grade MAC is significantly higher than that of high-grade MAC[4]. At the same time, the lack of MUC5AC expression is an indication of more aggressive colorectal tumors, as patients with negative MUC5AC expression have a poorer prognosis than those with positive expression[49]. However, it has been shown that MUC5AC promotes tumorigenicity through the transmembrane protein CD44, enhances the proliferation, invasion, and migration of CRC, and plays a positive role in maintaining specific subsets of cancer stem cell populations[50]. Therefore, the expression of MUC5AC and its mechanism in colorectal MAC need to be further studied.

### Genetic origins

There are two main pathways for the occurrence of CRC (Figure 2)[51,52]: The conventional adenoma-carcinoma pathway, which accounts for 70%-80% of CRC cases. Usually mutations in *APC*, *KRAS* and *TP53*, account for 60%, 45% and 54% of cases, respectively. The other is the serrated pathway, which accounts for 20%-30% of CRC cases and usually has a high frequency of *BRAF* mutations (70%-100%), CIMP-H, and high MSI (MSI-H)[53-55]. A meta-analysis of 46 studies involving 17 746 patients demonstrated that MAC had higher *KRAS* [odds ratio (OR) = 1.46, 95%CI: 1.08-2.0,  $P = 0.014$ ], *BRAF* (OR = 3.49, 95%CI: 2.50-4.87,  $P < 0.001$ ), higher MSI (OR = 3.98, 95%CI: 3.30-4.79,  $P < 0.001$ ), and CIMP-H (OR = 3.56, 95%CI: 2.85-4.43,  $P < 0.001$ ), and lower p53 expression (OR = 0.46, 95%CI: 0.31-0.67;  $P < 0.001$ ) compared to NMAC, which suggests that the genetic origin of MAC is primarily associated with the serrated pathway[56]. Some researchers have proposed that MAC can be divided into two subtypes. The first type, characterized by MSI, is mostly confined to the proximal colon, usually presents with loss of expression of hMLH1 and p27, and has a good prognosis. The second subtype, characterized by microsatellite stability, is more common in the distal colon and rectum, with normal expression of hMLH1 and p27, and a poor prognosis[57].



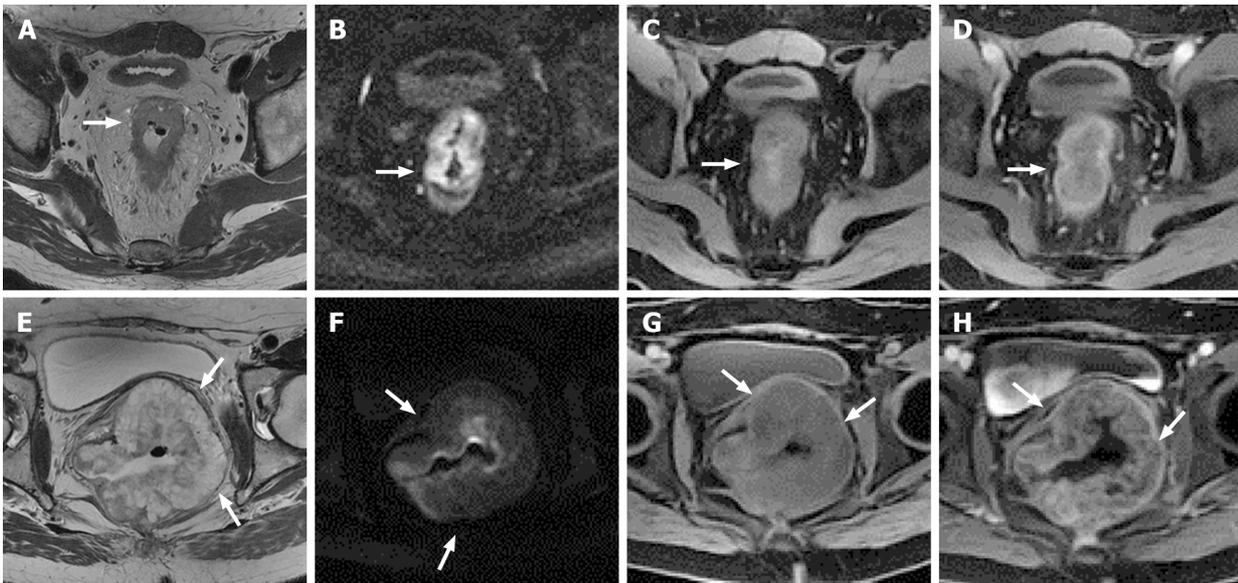
**Figure 2** Main pathways for the occurrence of colorectal cancer and the genetic and epigenetic features involved in the development of colorectal cancer. CRC: Colorectal cancer; MMR: Mismatch repair; MVHP: Microvesicular hyperplastic polyp; SSL: Sessile serrated lesion; SSL-D: Sessile serrated lesion with dysplasia; MSI: Microsatellite instability; MSS: Microsatellite stability; GCHP: Goblet cell-rich hyperplastic polyp; TSA: Traditional serrated adenoma; TSA-HGD: Traditional serrated adenoma with high-grade dysplasia.

MSI is present in 15% of CRC cases[58], of which 3%[59] are present in Lynch syndrome, and 12% are sporadic cancers[60]. Currently, four pathogenic genes associated with Lynch syndrome have been characterized namely *MSH2* plus *EPCAM*, *MLH1*, *MSH6* and *PMS2*. Germline mutations in *MLH1* and *MSH2* account for most cases (60%-80%), with a limited number of Lynch syndrome cases with germline mutations in *MSH6* and *PMS2*, and particularly rare germline *EPCAM* mutations that epigenetically inactivate *MSH2*[61]. Sporadic MSI CRC is primarily caused by acquired methylation in the promoter region of the *MLH1* gene[60]. The association of *BRAF* mutations (usually *V600E* mutations) with MSI and CIMP-H has been well established [62]. *BRAF* mutations are extremely rare in Lynch syndrome[63], suggesting that MSI in MAC is primarily sporadic.

## DIAGNOSIS

Currently, the diagnosis of MAC is primarily based on computed tomography (CT), magnetic resonance imaging (MRI), colorectal endoscopy, or postoperative pathological biopsy. Compared to NMAC and SRCC, CT of MAC shows more heterogeneous enhancement (MAC *vs* NMAC *vs* SRCC, 95.8% *vs* 54.1% *vs* 32.8%), larger attenuation area (greater than two thirds of the tumor tissue, 54.2% *vs* 5.9% *vs* 3.0%), and more calcification (17.9% *vs* 6.8% *vs* 3.0%)[64].

MRI can distinguish MAC from NMAC, which facilitates early diagnosis of MAC rather than relying on postoperative histopathological diagnosis. Since NMAC shows moderate signal intensity on T2-weighted imaging (T2WI), mucus displays low signal intensity on T1-weighted imaging, whereas T2WI shows high signal intensity (similar to or higher than that of the rectum fat signals) (Figure 3)[65]. MRI has an accuracy of 96%-97%, a sensitivity of 94%-100%, and a specificity of 95%-98% in diagnosing histological types of mucus[66]. Stanley *et al* believed that MRI was superior to preoperative biopsy for MAC diagnosis[67]. Before treatment, MRI diagnosed 60/330 (18%) mucinous rectal cancer cases, and initial biopsy diagnosed 15 (5%) (diagnostic OR = 4.67, *P* < 0.05) cases. The 60 patients who underwent surgery were ultimately confirmed to have mucinous tumors using histopathological analysis. MRI has great advantages not only in the diagnosis of MAC, but also in predicting the response of MAC to neoadjuvant therapy. Cao *et al*[68] used preoperative T2WI to clarify the mucus pool (high signal) and tumor solid components (medium signal), and classified MAC into two types: mixed type, where the mucus was rich in solid tumor components, and separated type, where the secretory mucus component was located



**Figure 3** Magnetic resonance imaging of rectal adenocarcinoma and mucinous adenocarcinoma. A-D: Rectal adenocarcinoma; E-H: Rectal mucinous adenocarcinoma. A: Axial non-lipid-suppressing T2-weighted imaging (T2WI) showing irregular circumferential thickening of the rectal wall, with slightly higher T2WI signal, lower than that of fat; B: Diffusion-weighted imaging (DWI) showing that the lesion was high signal; C: Low signal on plain T1-weighted imaging (T1WI); D: Axial enhanced T1WI showing moderate to high enhancement of the tumor; E: Axial non-lipid-suppressive T2WI showing that the rectal wall was thickened approximately three quarters of the circumference, and the left side wall was mainly with high signal on T2WI, which was close to the fat T2 high signal, with a low signal interlaced distribution; F: DWI showing that the lesion was mainly high signal; G: Low signal on plain T1WI; H: Axial enhanced T1WI showing enhanced tumor margins and low internal enhancement.

outside the solid tumor, to predict the response of locally advanced rectal MAC to neoadjuvant therapy, since patients with mixed-type mucin pool showed a lower tumor response rate than those with separate type mucin pool following neoadjuvant chemotherapy (4.9% *vs* 25.5%,  $P = 0.002$ ). However, using MRI to diagnose MAC can also produce false-positive results, possibly attributed to edema, congestion, abscess, or necrosis. False positives are especially important after treatment, as submucosal edema appears in the normal rectal wall after radiotherapy and chemotherapy[69]. More importantly, a few patients with CRC may form acellular mucin pools following adjuvant treatment, which is a manifestation of tumor response to treatment and is usually associated with a better prognosis[70,71]. However, due to the T2WI high signal on MRI, it is difficult to distinguish between persistent cell mucins (residual MAC tissue lacking response) and acellular mucin pools (therapeutic effect). There is currently no imaging technique to distinguish between the two[72], hence the comparison of MRI before and after treatment is particularly important.

Positron emission tomography (PET)/CT is an effective auxiliary test for patients with complicated conditions and cannot be clearly diagnosed by routine examination to determine the presence of distant metastases[73]. Although some studies have found no significant difference in the uptake of 18-fluorodeoxyglucose (FDG) between rectal MAC and NMAC in PET[74,75], it is not uncommon that MAC shows low uptake of 18-FDG on PET/CT and PET/MRI, and that the 18-FDG affinity of the tumor on a PET scan is inversely proportional to the total amount of mucins, which may lead to false-negative results[76].

Extracellular mucinous components > 50% are usually estimated by pathologists, while mucinous components vary in different pathological sections of the same tumor. In addition, Li *et al*[77] observed no significant difference in the distribution of mutations among the three adenocarcinoma subgroups with mucin characteristics (< 30%, 30%-50%, and > 50% mucinous components in tumor tissue)[77]. Furthermore, the more extracellular mucinous components of MAC tissue (50%-79%, 80%-89% and  $\geq 90\%$ ), the worse the patient's OS and recurrence-free survival[78]. These findings suggest that more objective and standardized histopathological analysis and molecular data are warranted to update the classification of MAC and adenocarcinoma with mucinous components.

## TREATMENT

The existing guidelines for the diagnosis and treatments of CRC are primarily based on TNM staging, biomarkers including *BRAF*, *RAS*, *HER2* and microsatellite status [73], and do not make recommendations based on the characteristics of MAC. Differences in histopathology and molecular characteristics between MAC and NMAC influence their treatment and prognosis, therefore, establishing standards for the diagnosis and treatments of MAC is essential.

### **Surgery, radiotherapy, and chemotherapy**

Studies on patients with stage II or III colon cancer receiving adjuvant chemotherapy after radical resection have reported no significant difference in OS (HR = 1.05, 95% CI: 1.02-1.08,  $P < 0.001$ ) between patients with stage II NMAC and MAC [79,80], whereas in patients with stage III colon cancer, compared to NMAC, the OS (HR = 1.05, 95% CI: 1.02-1.08,  $P < 0.001$ ) [79], cancer-specific survival (CSS) (5-year CSS rate: MAC *vs* NMAC, 72.7% *vs* 67.9%,  $P < 0.0001$ ) [81] and disease-free survival (HR = 1.82, 95% CI: 1.03-3.23,  $P = 0.04$ ) [82] of MAC were significantly decreased. Studies on patients with stage IV CRC receiving palliative chemotherapy illustrated that despite the different chemotherapy regimens used in these trials [5-fluorouracil (5-FU) with oxaliplatin and/or CPT-11 [83], FOLFOX-4 regimen [84], CAP + oxaliplatin + bevacizumab with or without cetuximab [85], 5-FU-based first-line chemotherapy [12]], the median OS of patients with MAC was shorter than that of patients with NMAC (MAC *vs* NMAC, 14.0 mo *vs* 23.4 mo, 8.0 mo *vs* 18.0 mo, 13.1 mo *vs* 21.5 mo, 11.8 mo *vs* 17.9 mo, respectively). However, although patients with stage III and IV MAC have poor responses to adjuvant or palliative chemotherapy, current evidence shows that adjuvant chemotherapy can effectively improve the survival rate of patients with stage II and III MAC [79,81].

A meta-analysis that included eight comparative series on the association between mucinous histology and response to neoadjuvant chemoradiotherapy in rectal cancer reported that MAC had a reduced rate of pathological complete response (pCR) (OR = 0.078, 95% CI: 0.015-0.397,  $P = 0.002$ ) and tumor downstaging (OR = 0.318, 95% CI: 0.185-0.547,  $P < 0.001$ ) following neoadjuvant chemoradiotherapy with an increased rate of positive resection margins (OR = 5.018, 95% CI: 3.224-7.810,  $P < 0.001$ ) and poor OS (OR = 1.526, 95% CI: 1.060-2.198,  $P = 0.023$ ) following resection, which suggests mucinous histology of rectal MAC as a biomarker for poor prognosis after neoadjuvant chemoradiotherapy [86,87]. Approximately 30% of patients with rectal cancer who received neoadjuvant therapy can have a clinical complete response. At this time, a watch-and-wait strategy can be adopted to provide patients with the opportunity to preserve the rectum and avoid surgery [88]. Tan *et al* [87] discovered that patients with NMAC (21%) were more likely to achieve pCR ( $P < 0.001$ ) than those diagnosed with MAC (14%); in patients who achieved pCR, those with MAC had a poorer survival, with a 3-year OS rate of 67.5%, while the 3-year OS of patients with NMAC was 93.8% ( $P < 0.001$ ) [87]. Therefore, the watch-and-wait strategy should be used more cautiously in patients with MAC. For patients with rectal MAC, preoperative treatment (short-term preoperative radiotherapy and preoperative chemoradiotherapy) plus total mesorectal resection (TME) [89] or adjuvant chemotherapy after TME [90] can be used to narrow the survival gap between rectal MAC and NMAC.

### **Hyperthermic intraperitoneal chemotherapy**

The peritoneum is associated with treatment failure in patients with CRC. However, due to lack of clinical follow-up and available imaging technology, the diagnosis cannot be made in the early stages, resulting in an inaccurate assessment of the incidence of peritoneal metastasis. Sugarbaker [91] recommended a combination of cytoreductive surgery (CRS) to remove all visible peritoneal metastases and hyperthermic intraperitoneal chemotherapy (HIPEC) to remove minimal residual disease. Since the peritoneal metastatic rate of patients with colorectal MAC is higher than that of patients with NMAC [14], CRS combined with HIPEC is particularly important. Multiple studies have shown that the survival benefit of CRS and HIPEC in patients with peritoneal metastasis caused by CRC is better than that of systemic chemotherapy alone [92,93]. However, the results of a recent multicenter, randomized clinical trial showed that adding HIPEC to CRS did not benefit patients with peritoneal metastatic CRC (HR = 1.00, 95% CI: 0.63-1.58,  $P = 0.99$ ), which resulted in more frequent postoperative late complications (CRS plus HIPEC group *vs* CRS group, 42% *vs* 32%,  $P = 0.083$ ) [94]. Therefore, CRS alone should be the cornerstone of

therapeutic strategies with curative intent for colorectal peritoneal metastases. CRS plus HIPEC should be selected after a careful and individualized assessment including Eastern Cooperative Oncology Group performance status scores, peritoneal cancer index, and previous chemotherapy lines. Klempner and Ryan[95] suggested that future studies of peritoneal cancer should be attentive to the rich translational opportunities that CRS can supply for multiple avenues of investigation.

### **Targeted therapy**

Traditional chemotherapy usually targets rapidly proliferating cancer cells by interfering with cell division. However, it also nonspecifically targets healthy cells that divide rapidly, such as bone marrow and hair cells, resulting in recognized chemotherapy side effects[96]. Therefore, the main goal of targeted therapy is to ensure that the drugs specifically act on tumor cells, while not affecting normal tissue cells. Currently, targeted drugs for CRC are primarily used in patients with advanced or metastatic CRC, including anti-epidermal growth factor receptor (EGFR) monoclonal antibody (cetuximab) and anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab). As previously mentioned, colorectal MAC has a higher frequency of *KRAS* and *BRAF* mutations, with the tumors being located more in the right hemicolon. De Roock *et al*[97] found that the median OS (32 wk *vs* 50 wk, HR = 1.75, 95%CI: 1.47-2.09,  $P < 0.0001$ ) and median progression-free survival (PFS) (12 wk *vs* 24 wk, HR = 1.98, 95%CI: 1.66-2.36,  $P < 0.0001$ ) of patients with *KRAS* mutations treated with cetuximab were lower than those of wild-type *KRAS* patients. In wild-type *KRAS* patients, the response rate of *BRAF* mutation carriers was significantly lower than that of *BRAF* wild-type-containing patients (8.3% *vs* 38.0%, OR = 0.15, 95%CI: 0.02-0.51,  $P = 0.0012$ ). Studies have also reported that patients with metastatic CRC harboring a mutation in *KRAS* or *NRAS* do not respond to anti-EGFR therapy. Therefore, activating *RAS* mutations were regarded as negative predictive biomarkers for anti-EGFR therapy[98-100]. Research on bevacizumab has shown that FOLFOXIRI plus bevacizumab is a viable treatment option regardless of the mutation status of *RAS* or *BRAF*[101]. In addition, in patients with wild-type *RAS* and *BRAF*, the effect of bevacizumab combined with chemotherapy in right hemicolon cancer was better than that of cetuximab combined with chemotherapy[73]. Therefore, in addition to patients with wild-type *RAS* and *BRAF* and whose tumors are located in the left hemicolon or rectum considering anti-EGFR monoclonal antibody plus chemotherapy as the first-line treatment, anti-VEGF monoclonal antibody plus chemotherapy might be a better treatment option for patients with advanced MAC.

Drugs targeting mucins, one of the prominent features of MAC, are potential treatment strategies currently being investigated. Ahmad *et al*[37] found that the MUC1-C inhibitor, GO-203, could inhibit the growth of colon cancer cells *in vitro* and in nude mice, primarily by downregulating the expression of the TP53-inducible glycolysis and apoptosis regulator protein. In addition, since mucins are a class of O-glycosylated glycoproteins, the aberrant expression of O-glycan synthesis enzyme core 2 1,6 N-acetylglucosaminyltransferase (GCNT3/C2GnT-2) can lead to overexpression of mucins[102]. Therefore, targeting GCNT3 can inhibit mucin synthesis in MAC. At present, small-molecule GCNT3 inhibitors are under development[103].

### **Immunotherapy**

The interaction of programmed cell death (PD)-1 on T cells and its interaction with its ligand, PD-L1, expressed on tumor cells and immune cells, including B cells, dendritic cells, and macrophages, plays an important role in immune checkpoint suppression [104]. The binding of PD-L1 on tumor cells to PD-1 on the surface of T cells inhibits T-cell-mediated antitumor immunity[105]. Immune checkpoint inhibitors have significantly improved the long-term outcomes of a few malignant tumors, such as melanoma, lung cancer, and renal cell carcinoma[106-108]. In MAC, the expression of PD-L1 in tumor cells and tumor-infiltrating immune cells is increased[109], which may be related to the high proportion of MSI-H in MAC. Studies have shown that compared to tumors with proficient mismatch repair (pMMR), tumors with deficient MMR (dMMR) highly express immune checkpoint proteins, including PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein (CTLA)-4[110]. MSI CRC has a higher tumor-infiltrating lymphocyte density and prominent Crohn's-like lymphoid reaction than MSS CRC[111,112]. It has been previously believed that the increased levels of neoantigens produced by frameshift mutations also increase T cell infiltration in MSI CRC. Recent findings have supported this hypothesis, linking the number of frameshift mutations directly to the density of tumor-infiltrating lymphocytes[113]. Based on these observations, several clinical trials are studying the application of PD-1 immunotherapy in MSI CRC. Le *et al*[110] found that the efficacy of pembrolizumab in

dMMR CRC was far better than that of pMMR CRC in terms of immune-related objective remission rate (40% *vs* 0%) and immune-related PFS rate within 20 wk (78% *vs* 11%)[110]. Therefore, pembrolizumab was the first drug that did not consider tumor types and only used biomarkers (dMMR/MSI-H) as treatment options based on overall response rates. Additional data also showed that nivolumab had benefits in advanced dMMR/MSI-H CRC where previous cytotoxic drugs had failed, with 31% of cases responding, and 69% of the overall disease control rate[114]. Therefore, the National Comprehensive Cancer Network guidelines have officially recommended pembrolizumab or nivolumab as second-line or third-line treatment for patients with MSI-H metastatic CRC since 2017[115]. Michael *et al*[116] reported that compared to anti-PD-1 monotherapy, nivolumab combined with ipilimumab had a higher response rate and better long-term clinical benefits, with controllable safety, and thus, should be considered as the first-line treatment for patients with metastatic dMMR/MSI-H CRC. The KEYNOTE-177 trial found that when pembrolizumab was used as the first-line treatment for metastatic dMMR/MSI-H CRC, patients had a significantly longer PFS (median, 16.5 *vs* 8.2 mo, HR = 0.60, 95%CI: 0.45-0.80,  $P = 0.0002$ ) and fewer treatment-related adverse events (22% *vs* 66%) compared to those receiving chemotherapy[117]. Therefore, the US Food and Drug Administration approved pembrolizumab as a first-line treatment for unresectable or metastatic dMMR/MSI-H CRC in June 2020[118]. However, a subgroup analysis in the KEYNOTE-177 trial indicated that patients with metastatic dMMR/MSI-H CRC with *KRAS* or *NRAS* mutations could not benefit from pembrolizumab alone[117]. Whether adding chemotherapy or anti-CTLA-4 to PD-1 blockade could overcome this apparent resistance remains unknown.

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## PROGNOSIS

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The prognosis of patients with colorectal MAC remains controversial, which may be due to the higher TNM stage at the time of diagnosis. Studies have found that the 5-year OS rate of patients with MAC was lower than that of patients with NMAC, whereas no difference in prognosis was found when comparing patients with the same TNM stage[11,24,27]. However, other studies have indicated that in stage III colon cancer, patients with MAC have a poor 5-year CSS rate (MAC *vs* NMAC, 67.9% *vs* 72.7%)[81]. Catalano *et al*[119] believed that the controversy over the prognosis of colorectal MAC was caused by the poor prognosis of rectal MAC, while there was no significant difference between colonic MAC and NMAC. The authors also found, for patients with stage II and III colon cancer who underwent radical surgery, there was no significant difference in prognosis between MAC and NMAC. In addition, MAC is more likely to have nodal metastases, be diagnosed at an advanced stage, and have lower resectability of tumors in the rectum than the colon, thus leading to a poor prognosis of rectal MAC[119].

Studies have also demonstrated that higher age (> 65 years), tumor grades including moderately, poorly, and undifferentiated tumors, tumor location in the rectum, preoperative CEA level (> 5 ng/mL), higher pathological T or N stage, intestinal obstruction, and perineural infiltration were all significantly associated with poor OS in MAC[7,120]. A greater number of lymph nodes examined (no fewer than 12) significantly increased OS (HR = 0.601, 95%CI: 0.537-0.673,  $P < 0.001$ ) and CSS (HR = 0.582, 95%CI: 0.511 to -0.664,  $P < 0.001$ ) in patients with colorectal MAC[120]. *BRAF* mutations were significantly associated with CRC-specific mortality (multivariate HR = 1.64, 95%CI: 1.18-2.27,  $P = 0.003$ ), while MSI-H was associated with a statistically significant reduction in CRC-specific mortality (multivariate HR = 0.28, 95%CI: 0.17-0.46,  $P < 0.001$ ). Considering both MSI-H and *BRAF*, the 5-year CSS rates were 79%, 73%, 65%, and 46%, respectively, in MSI-H/*BRAF*-wild-type, MSI-H/*BRAF*-mutant, MSS/*BRAF*-wild-type, MSS/*BRAF*-mutant[121], suggesting that the prognosis of patients with MAC could be stratified according to the status of MSI-H combined with *BRAF*. Notably, in metastatic CRC, dMMR corresponds to a poorer prognosis compared with pMMR[122]. Immunotherapies, including anti-PD-1 and CTLA-4, emerged in recent years are promising treatment strategy.

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## CONCLUSION

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Colorectal MAC is a unique clinicopathological subtype of CRC. This review comprehensively describes the clinicopathological characteristics, molecular features, diagnosis, treatment, and prognosis of colorectal MAC. One of the most notable

features of MAC is the aberrant expression of multiple mucins, but the underlying mechanism remains unclear. The mucinous features of MAC suggest that it originates from cells expressing MUC2, with no clear understanding of the mechanism underlying mucus production by MAC against radiotherapy and chemotherapy. In the future, in-depth research is needed to clarify the role of mucus in MAC. Colorectal MAC has a higher frequency of *KRAS*, *BRAF* mutations, CIMP-H, and MSI-H, suggesting that the genetic origin of colorectal MAC is mainly related to the serrated pathway of CRC, namely the *BRAF*, *MSI*, and *CIMP* pathways, which also explains the high proportion of MSI-H in MAC. MSI-H indicates a better response to immunotherapy, which is hopeful for patients with MAC. The prognosis of patients with colorectal MAC remains controversial, which may be attributed to the poor prognosis of rectal MAC, while there is no significant difference in the prognosis of colonic MAC and NMAC.

In summary, MAC has various clinicopathological and molecular characteristics that differ from those of NMAC. Therefore, personalized diagnosis and treatment of MAC is beneficial. Further studies, such as targeted drugs for mucins, sensitization to chemoradiotherapy, and immunotherapy, are warranted to improve the prognosis of patients with MAC.

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