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Review article

THE ROLE OF THE MUCINOUS COMPONENT AS AN INDEPENDENT PREDICTIVE FACTOR IN COLORECTAL ADENOCARCINOMA THERAPY - THE POTENTIAL OF ARTIFICIAL INTELLIGENCE AS AN ADJUNCT TOOL TO IMPROVE TREATMENT OUTCOMES

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Abstract: Mucinous adenocarcinoma of the colon (MAC) is a distinct histological subtype of colorectal cancer (CRC), defined by the presence of ≥ 50% extracellular mucin. This CRC subtype exhibits unique clinical and molecular characteristics, including more frequent localization in the right colon, higher prevalence among younger patients, and associations with microsatellite instability-high (MSI-H) and BRAF gene mutations. Evidence suggests that MAC demonstrates a poorer response to conventional therapies; however, the independent prognostic value of the mucinous component remains unclear.

This narrative review aims to evaluate the prognostic significance of the mucinous component in CRC. Twenty relevant studies published between 2018 and 2025 were analyzed. Results indicate that MAC is more often detected at advanced stages and shows a weaker response to fluorouracil-based regimens and neoadjuvant chemoradiotherapy in rectal tumors. Nonetheless, several studies reported no significant difference in overall survival between mucinous and non-mucinous carcinomas. Additionally, immune-related factors such as tumor-infiltrating lymphocytes (TILs) and desmoplasia are gaining importance and may have greater prognostic value than mucinous differentiation itself.

MAC also frequently exhibits marked molecular heterogeneity, complicating prognosis and treatment decisions. Consequently, careful patient monitoring and timely molecular profiling are essential for optimizing therapy. Novel artificial intelligence–based models that integrate histological images, molecular biomarkers, and clinical data show promise for personalizing treatment in MAC.

In conclusion, although MAC is currently treated according to standard CRC guidelines, its distinct features underscore the need for individualized therapeutic approaches and further clinical research.

Keywords: mucinous adenocarcinoma, colorectal cancer, prognosis, MSI-H, treatment response.

INTRODUCTION

Colorectal cancer (CRC) is among the leading causes of cancer incidence and mortality worldwide, particularly in countries with medium to high socioeconomic status. Mucinous adenocarcinoma of the colon (MAC) is a distinct histological subtype of CRC, defined by the presence of ≥ 50% extracellular mucin within the tumor. This subtype is characterized by specific features, including preferential localization in the right colon, higher prevalence among younger patients, high microsatellite instability (MSI-H), BRAF gene mutations, and a generally poorer response to therapy, especially fluorouracil-based chemotherapy (1).

In contrast to non-mucinous adenocarcinomas, which often show different biological behavior and clinical outcomes, mucinous adenocarcinomas exhibit notable heterogeneity and distinct patterns of invasion and metastasis. However, the independent prognostic significance of the mucinous component remains a subject of ongoing debate.

The aim of this paper is to explore the prognostic potential of the mucinous component in colon adenocarcinoma through a narrative review of recent literature and to evaluate its clinical relevance.

Histopathological and Molecular Characteristics of Mucinous Adenocarcinoma

Mucinous adenocarcinoma of the colon (MAC) represents a histologically distinct and biologically unique subgroup of colorectal cancer (CRC), with its presence significantly influencing clinical presentation, therapeutic response, and disease outcomes. Defined by the presence of ≥ 50% extracellular mucin in tumor tissue, MAC encompasses a complex biological background beyond its histological classification.

Numerous studies suggest that MAC is not simply a histological variant but a tumor type marked by a distinct molecular profile and immune microenvironment, which poses challenges for standard treatment protocols and raises important questions about its independent prognostic value.

Epidemiological data indicate that MAC occurs more frequently in the right colon and among younger patients, often diagnosed at advanced stages (2–5). Analyses of the SEER database confirm that mucinous tumors are more commonly identified at stages III and IV, reflecting their aggressive clinical behavior (3, 5). Additionally, MAC is more frequently associated with high microsatellite instability (MSI-H) and BRAF mutations, which contribute to its biological uniqueness and have important therapeutic implications (1, 6).

However, the molecular heterogeneity within MAC raises the question of whether all mucinous adenocarcinomas should be regarded as a single homogeneous group.

Immune Microenvironment and Prognostic Indicators

Beyond molecular factors, the immune landscape of MAC has attracted increasing attention. Tumor-infiltrating lymphocytes (TILs) hold particular prognostic significance as strong predictors of survival. Fadel et al. emphasize that the density of lymphocytic infiltration and the presence of desmoplasia have greater predictive value for survival than mucinous differentiation alone (3). High lymphocyte density correlates with a more robust immune response and better prognosis, whereas desmoplasia — reactive fibrous proliferation surrounding the tumor — is linked to a more aggressive disease phenotype and poorer outcome.

Kepil et al. thoroughly characterized the immune phenotype of mucinous tumors, highlighting significant differences in the expression of immune markers (PD-L1, CD8+ T-cells, macrophages CD68 and CD163) compared to non-mucinous tumors (7). These alterations suggest distinct immune evasion mechanisms and potentially differential responses to immunotherapy. Methodologically, the study employed immunohistochemistry to precisely localize and quantify these markers, contributing to the reliability of findings and advancing understanding of the mucinous tumor microenvironment.

Controversies in Prognosis and Therapeutic Implications

Prognostic data for MAC remain heterogeneous. Kim et al. reported poorer prognosis and diminished response to adjuvant chemotherapy in stages II and III compared to non-mucinous tumors (4). Conversely, Huang et al. and Dai et al. found no significant differences in outcomes at earlier disease stages (8, 9). These findings suggest that mucinous histology alone is insufficient as an independent prognostic factor, underscoring the need to integrate molecular, histological, and immune parameters.

Chemotherapy Resistance and Limitations of Standard Treatment

Therapeutic response in MAC further complicates clinical management. Standard CRC regimens include FOLFOX, CAPOX, and FOLFIRI; however, MAC tumors often exhibit resistance to fluorouracil-based therapies, especially those with MSI-H and BRAF mutations (1, 6–11). A meta-analysis by McCawley et al. demonstrated that mucinous rectal adenocarcinoma responds significantly worse to neoadjuvant chemoradiotherapy, evidenced by lower pathological regression, higher rates of positive surgical margins, and inferior overall prognosis compared to non-mucinous tumors (10). These differences are attributed to the unique biological properties and microenvironment of mucinous tumors, highlighting the necessity for individualized therapeutic approaches.

While RAS wild-type status remains a key criterion for selecting patients for anti-EGFR therapy, Moretto et al. showed that the presence of a mucinous component may substantially reduce the efficacy of this treatment even in patients with molecular markers of sensitivity (11). This suggests that tumor histological subtype independently influences therapeutic response, advocating for an integrated approach that incorporates both molecular and histopathological tumor characteristics.

Secondary Tumor Risk and Surveillance Considerations

Wu et al. analyzed the risk of secondary malignancies in patients with various CRC histological subtypes, including MAC, and identified specific patterns of new tumor development with elevated risks for certain secondary primary tumors (12). These findings emphasize the need for vigilant long-term follow-up and consideration of histological subtype in secondary prevention strategies.

Emerging Role of Immunotherapy in MSI-H Mucinous CRC

Immunotherapy, particularly anti-PD-1 blockade, shows significant promise in MSI-H mucinous carcinomas, offering novel treatment options for this subgroup characterized by poor chemotherapy response. Interest in applying artificial intelligence (AI) and radiomics for personalized therapy is rapidly increasing, as these approaches enable integration of multidimensional data and more precise prediction of therapeutic outcomes.

Radiomics and Artificial Intelligence in Precision Oncology

Radiomics—the quantitative analysis of medical imaging data (CT, MRI)—combined with AI facilitates prediction of tumor molecular features (KRAS, NRAS, BRAF mutations) and assessment of treatment response. Yang et al. successfully predicted these mutations using CT-based radiomics (13). Shaish et al. demonstrated that MRI-radiomics can predict response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer (14). Li et al. developed machine learning models to preoperatively predict perineural invasion and KRAS mutation, with direct clinical applications (15). Within the ATTRACT study, Caruso et al. applied radiogenomics to identify high-risk colorectal tumors, paving the way for integrated strategies to detect biologically aggressive MACs (16, 17). Golia Pernicka et al. showed that MSI status can be predicted using radiomics from baseline CT scans (18), while Abbaspour et al. successfully predicted lymph node metastasis preoperatively with radiomics (19).

Although these data confirm the considerable potential of radiomics and AI in optimizing MAC therapy, widespread clinical implementation requires further research, methodological standardization, and validation through prospective multicenter studies.

CONCLUSION

Mucinous adenocarcinoma of the colon represents a biologically and clinically distinct subgroup of colorectal cancer, characterized by unique molecular, histological, and immunological features that significantly influence therapeutic response and potentially impact patient survival. Although multiple studies have reported a poorer prognosis associated with MAC, especially in advanced disease stages, the prognostic value of the mucinous component alone remains controversial and appears to be modulated by additional factors such as molecular alterations and the tumor immune microenvironment.

The integration of molecular biomarkers—including MSI status, BRAF and RAS mutations—with immune indicators like tumor-infiltrating lymphocytes and immune checkpoint expression offers a promising avenue for personalizing therapeutic strategies in this subgroup. Moreover, emerging technologies such as radiomics and artificial intelligence hold considerable potential to enhance preoperative tumor characterization, predict treatment response, and refine risk stratification.

To translate these advances into clinical practice, further prospective, multicenter studies are required to validate stratification models and optimize tailored treatment protocols specifically for patients with mucinous adenocarcinoma. Such efforts are essential to improve clinical outcomes and advance precision oncology for this challenging CRC subtype.

Abbreviations

AI – Artificial Intelligence
CAPOX – Capecitabine and Oxaliplatin
CRC – Colorectal Cancer
CT – Computed Tomography
EGFR – Epidermal Growth Factor Receptor
FOLFIRI – 5-Fluorouracil, Leucovorin, and Irinotecan
FOLFOX – 5-Fluorouracil, Leucovorin, and Oxaliplatin
MAC – Mucinous Adenocarcinoma of the Colon
MRI – Magnetic Resonance Imaging
MSI-H – Microsatellite Instability-High
PD-1 – Programmed Cell Death Protein 1
PD-L1 – Programmed Death-Ligand 1
RAS – Rat Sarcoma Viral Oncogene Homolog
SEER – Surveillance, Epidemiology, and End Results (database)
TILs – Tumor-Infiltrating Lymphocytes

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study.

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

ULOGA MUCINOZNE KOMPONENTE KAO NEZAVISNOG PREDIKTIVNOG FAKTORA U TERAPIJI ADENOKARCINOMA KOLONA-POTENCIJAL VEŠTAČKE INTELIGENCIJE KAO POMOĆNOG ALATA ZA UNAPREĐENJE ISHODA LEČENJA

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Mucinozni adenokarcinom kolona (MAC) je posebna histološka varijanta kolorektalnog karcinoma (CRC), definisana prisustvom ≥ 50% ekstracelularnog mucina. Ovaj podtip CRC-a ima različite kliničke i molekularne karakteristike, kao što su češća lokalizacija u desnom kolonu, viša prevalence kod mlađih pacijenata, prisustvo mikrosatelitske nestabilnosti (MSI-H), kao i mutacije u BRAF genu. Postoje indicije da MAC pokazuje slabiji odgovor na konvencionalne terapije, ali ostaje pitanje da li mucinozna komponenta ima nezavisan prognostički značaj.

U ovom radu prikazan je narativni pregled literature sa ciljem procene prognostičke vrednosti mucinozne komponente kod CRC. U analizu je uključeno 20 relevantnih studija objavljenih u periodu od 2018. do 2025. godine. Rezultati ukazuju da MAC češće biva otkriven u uznapredovalim stadijumima bolesti i pokazuje slabiji odgovor na fluorouracil-bazirane protokole i neoadjuvantnu radiohemoterapiju kod rektalnih tumora. Ipak, nekoliko studija nije pronašlo značajnu razliku u ukupnom preživljavanju između mucinoznih i nemucinoznih karcinoma. Pored toga, sve veći značaj imaju imunološki faktori kao što su prisustvo TILs i desmoplazije, koji mogu nadmašiti prognostički uticaj same mucinozne diferencijacije.

Zapaženo je i da MAC često pokazuje izraženiju molekularnu heterogenost, što dodatno komplikuje prognozu i terapijski pristup. U tom kontekstu, pažljivo praćenje bolesnika i pravovremena molekularna karakterizacija postaju od ključnog značaja za optimalno lečenje. Novi modeli zasnovani na veštačkoj inteligenciji, koji integrišu histološke slike, molekularne biomarkere i kliničke podatke, ukazuju na potencijal u personalizaciji terapije za MAC. U zaključku, iako se MAC leči prema važećim CRC smernicama, njegove specifičnosti ukazuju na potrebu za individualizovanim terapijskim pristupom i daljim kliničkim istraživanjima.

***Ključne reči**:* mucinozni adenokarcinom, kolorektalni karcinom, prognoza, MSI-H, terapijski odgovor.

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