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Primary Tumor Site Modifies the Prognostic Impact of Mucinous Histology in Non-metastatic Colorectal Cancer: An Interaction Analysis of the SEER Database

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Abstract

Objectives: The prognostic value of mucinous adenocarcinoma (MAC) in colorectal cancer (CRC) remains controversial, with conflicting reports regarding its impact on survival. We hypothesized that the primary tumor location would modify the prognostic significance of mucinous histology in patients with non-metastatic CRC.

Methods: We analyzed 286.046 adult patients with non-metastatic CRC, identified in the surveillance, epidemiology, and end results database (2010-2022). Patients were stratified by histology (MAC vs. non-MAC) and tumor site (colon vs. rectum). Multivariable Cox proportional hazards regression was performed to evaluate overall survival (OS), adjusting for demographic and clinical covariates. A formal interaction term (histology×location) was included to assess effect modification.

Results: Among the total cohort, 17.096 (6.0%) patients exhibited MAC. Compared with non-mucinous tumors, mucinous tumors were significantly associated with advanced stage, higher grade, and female sex ($p<0.001$). Multivariable analysis identified MAC [hazard ratio (HR): 1.373; 95% confidence interval (CI): 1.326-1.422] and rectal location (HR: 1.066; 95% CI: 1.027-1.106) as independent predictors of mortality. Importantly, a significant interaction was detected between mucinous histology and rectal location (HR: 1.289; 95% CI: 1.203-1.381; $p<0.001$), indicating that the negative prognostic effect of MAC is amplified in rectal tumors. Consequently, 5-year OS was lowest for rectal MAC (55.1%) compared with colonic MAC (61.1%) and non-mucinous subtypes (colon: 68.5%; rectum: 68.7%) ($p<0.001$).

Conclusion: Primary tumor location significantly modified the prognostic impact of mucinous histology. The survival disadvantage of MAC is disproportionately severe in rectal cancer compared with colon cancer, suggesting that rectal MAC represents a distinct, aggressive entity requiring site-specific risk stratification and tailored management strategies.

Keywords: Colorectal cancer, mucinous adenocarcinoma, prognosis, SEER program

Introduction

Mucinous adenocarcinoma (MAC) represents a distinct histopathological subtype of colorectal cancer (CRC), accounting for approximately 10% to 20% of all cases (1). Histologically, MAC is defined by the presence of abundant extracellular mucin comprising more than 50% of the tumor volume (2). Beyond its morphological features, this subtype exhibits a unique molecular profile compared to non-MAC, characterized by the overexpression of MUC2, a higher frequency of microsatellite instability (MSI), and increased rates of *BRAF* mutations (3).

Despite these well-defined characteristics, the prognostic significance of mucinous histology remains a subject of ongoing debate (4). While several studies identify MAC as an independent adverse prognostic factor, others suggest that the

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survival disparity disappears when adjusting for disease stage (2). Clinical management is further complicated by evidence suggesting that mucinous tumors display reduced sensitivity to standard treatments. Pharmacogenomic studies indicate that MAC often harbors mutations in genes such as *TYMP* and *ATP7B1*, which may confer resistance to 5-fluorouracil and oxaliplatin (2).

A critical factor that may elucidate these conflicting prognostic data is the primary tumor location. The colon and rectum are biologically distinct entities arising from different embryological origins, often described as a continuum of molecular alterations rather than a single disease (5). Consequently, the impact of mucinous histology may not be uniform throughout the colorectum. Previous literature suggests that while rectal MAC is consistently associated with poor outcomes, the prognostic value of colonic MAC remains controversial (2,4).

We hypothesized that the prognostic effect of mucinous histology is not static but is modified by the primary tumor site. Therefore, this study aimed to determine whether tumor location (colon vs. rectum) significantly modifies the prognostic impact of mucinous histology in patients with non-metastatic CRC.

Material and Methods

Data Source and Study Population

This retrospective cohort study used data from the surveillance, epidemiology, and end results (SEER) 17 registries research database (November 2024 submission), which covers approximately 26.5% of the United States population. Data were extracted using SEER*Stat software (version 9.0.42.0). Adult patients (≥18 years) diagnosed with CRC between 2010 and 2022 were identified. The year 2010 was selected to ensure the availability of contemporary staging and treatment variables. Patients were excluded if they had (1) primary tumors located outside the colorectum (e.g., anus or small intestine); (2) non-adenocarcinoma histology; (3) *in situ* disease, unknown stage, or diagnosis only by death certificate or autopsy; (4) appendiceal tumors, overlapping lesions, or colon not otherwise specified; (5) metastatic disease at diagnosis; (6) a non-first primary malignancy; or (7) missing survival time or follow-up data (Figure 1).

Variables and Definitions

The histologic subtype was defined using the histologic type variable of the International Classification of Diseases for Oncology, third edition. MAC was identified using codes 8480/3 and 8481/3, whereas all remaining adenocarcinoma histologies were classified as non-mucinous. Tumor location was derived from the primary site variable and categorized as colon (C18.0-C18.9) or rectum (C19.9-C20.9). Tumor extent

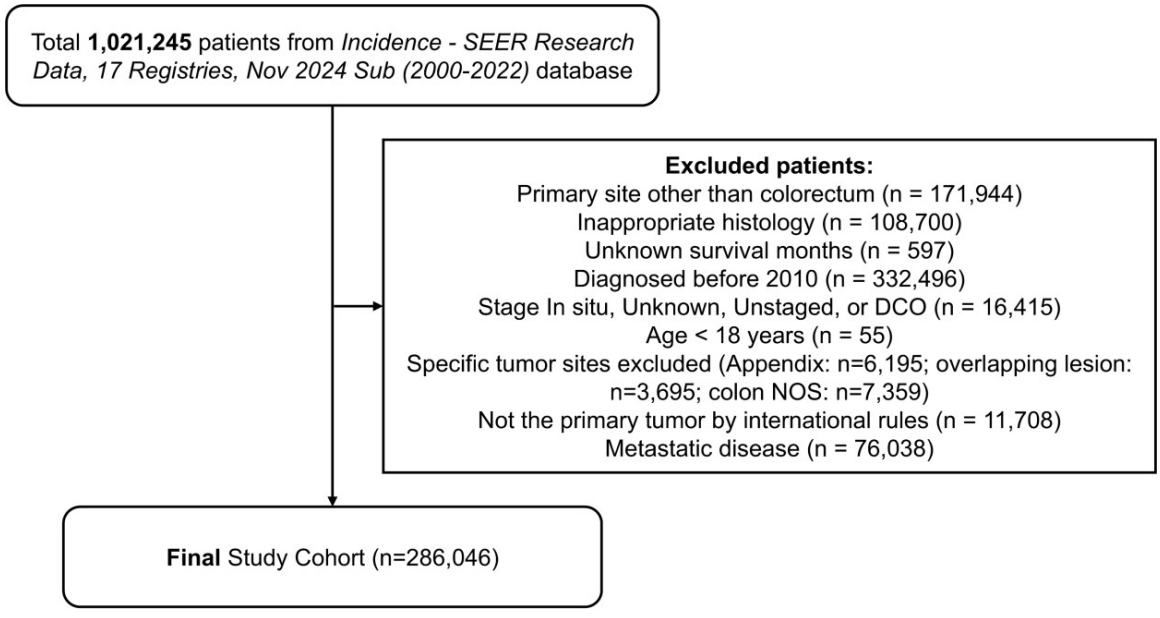

Figure 1. Study flow diagram

SEER: Surveillance, epidemiology, and end results, NOS: Not otherwise specified, DCO: Death certificate only

was determined using the SEER combined summary stage (2004+) with expanded regional codes and was dichotomized as node-negative (localized only or regional by direct extension only) versus node-positive (regional lymph node involvement with or without direct extension). Histological grade was grouped as well- or moderately differentiated versus poorly differentiated or undifferentiated. Treatment variables, including cancer-directed surgery, radiotherapy, and chemotherapy, were obtained from the SEER recode variables and dichotomized for analysis as "yes" versus "no/unknown". The primary endpoint was overall survival (OS), defined as the interval from diagnosis to death from any cause or to the last follow-up, based on the SEER survival months and vital status variables.

Statistical Analysis

Baseline characteristics were compared between histological groups using the chi-square test for categorical variables and the Student's t-test for continuous variables. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. To evaluate the independent association between histology and OS, a multivariable Cox proportional hazards regression model was constructed, adjusting for age, sex, race, stage, grade, surgery, radiotherapy, and chemotherapy. To test the hypothesis that the prognostic impact of mucinous histology differs by tumor site, a formal interaction term (histology×location) was included in the model. The proportional hazards assumption was verified using Schoenfeld residuals. All statistical analyses were performed using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Survival analyses were conducted using the survival and survminer packages. All tests were two-sided, with statistical significance set at $p<0.05$.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. SEER data are publicly available and de-identified; therefore, institutional review board approval and informed consent were not required. Access to the database was granted after signing the SEER data use agreement.

Results

Baseline Characteristics

A total of 286.046 patients with non-metastatic CRC were included, of whom 17.096 (6.0%) had MAC and 268.950 (94.0%) had non-mucinous tumors. Significant demographic differences were observed between the two groups; patients with MAC were older (mean age 68.7±14.1 vs. 66.4±13.4 years; $p<0.001$) and were more likely to be female (50.0% vs. 46.6%; $p<0.001$) and white (81.9% vs. 78.1%; $p<0.001$) compared to those with non-MAC tumors. Regarding tumor characteristics, MAC demonstrated a marked right-sided predominance: 63.8% of MAC cases were located in the right colon, compared with 40.8% of non-MAC tumors ($p<0.001$).

Conversely, primary rectal tumors were significantly less common in the MAC group (11.5%) than in the non-MAC group (23.8%). Histologically, mucinous tumors displayed more aggressive features at presentation, including a higher prevalence of stage III disease (41.2% vs. 34.6%; $p<0.001$) and a higher prevalence of poor differentiation (grade III-IV: 18.7% vs. 12.5%; $p<0.001$). Treatment patterns also varied: MAC patients underwent surgery more frequently (97.8% vs. 92.7%) but were less likely to receive radiotherapy than the non-MAC group (Table 1).

Multivariable Analysis and Interaction Assessment

To account for potential confounders, a multivariable Cox proportional hazards model was constructed (Table 2). After a median follow-up of 76 months, advanced age, male sex, stage III disease, high histological grade, and lack of surgery or of chemotherapy were identified as significant independent predictors of mortality ($p<0.001$ for all). The model revealed that both mucinous histology [hazard ratio (HR): 1.373, 95% confidence interval (CI): 1.326-1.422, $p<0.001$] and rectal location (vs. colon) (HR: 1.066, 95% CI: 1.027-1.106, $p=0.001$) were independent predictors of poorer OS. A significant interaction was observed between mucinous histology and rectal cancer (HR: 1.289, 95% CI: 1.203-1.381, $p<0.001$), indicating that the negative prognostic effect of MAC was significantly amplified in rectal tumors compared with colonic tumors.

Kaplan-Meier Survival Analysis

Kaplan-Meier curves, stratified by combined histology and tumor location, demonstrated significant differences in OS among the four subgroups (log-rank $p<0.001$) (Figure 2). Patients with non-mucinous tumors exhibited the most favorable survival outcomes, regardless of tumor location. In contrast, patients with mucinous histology demonstrated poorer survival, which was most pronounced in those with rectal primaries. The 5-year OS rates were 68.5% (95% CI: 68.2-68.7) for colon non-MAC; 68.7% (95% CI: 68.3-69.2) for rectum non-MAC; 61.1% (95% CI: 60.2-61.9) for colon MAC; and markedly lower for rectum MAC at 55.1% (95% CI: 52.7-57.5).

Table 1. Baseline characteristics of the study population stratified by histology

Characteristic	Total, n=286.046	MAC, n=17.096	Non-MAC, n=268.950	p-value*
Age, mean ± SD, years	66.5±13.5	68.7±14.1	66.4±13.4	**<0.001**
Age category, n (%) <65 years ≥65 years	 122.653 (42.9) 163.393 (57.1)	 6.025 (35.2) 11.071 (64.8)	 116.628 (43.4) 152.322 (56.6)	**<0.001**
Sex, n (%) Female Male	 133.810 (46.8) 152.236 (53.2)	 8.544 (50.0) 8.552 (50.0)	 125.266 (46.6) 143.684 (53.4)	**<0.001**
Race, n (%) White Other	 223.972 (78.3) 62.074 (21.7)	 13.998 (81.9) 3.098 (18.1)	 209.974 (78.1) 58.976 (21.9)	**<0.001**
Tumor location, n (%) Right colon Left colon Rectum	 120.557 (42.1) 99.510 (34.8) 65.979 (23.1)	 10.908 (63.8) 4.217 (24.7) 1.971 (11.5)	 109.649 (40.8) 95.293 (35.4) 64.008 (23.8)	**<0.001**
Stage, n (%) I-II III	 186.068 (65.0) 99.978 (35.0)	 10.058 (58.8) 7.038 (41.2)	 176.010 (65.4) 92.940 (34.6)	**<0.001**
Histological grade, n (%) I-II III-IV	 249.365 (87.2) 36.681 (12.8)	 13.902 (81.3) 3.194 (18.7)	 235.463 (87.5) 33.487 (12.5)	**<0.001**
Surgery, n (%) Performed Not performed/unknown	 266.078 (93.0) 19.968 (7.0)	 16.724 (97.8) 372 (2.2)	 249.354 (92.7) 19.596 (7.3)	**<0.001**
Radiotherapy, n (%) Yes No/unknown	 44.611 (15.6) 241.435 (84.4)	 1.638 (9.6) 15.458 (90.4)	 42.973 (16.0) 225.977 (84.0)	**<0.001**
Chemotherapy, n (%) Yes No/unknown	 103.020 (36.0) 183.026 (64.0)	 6.301 (36.9) 10.795 (63.1)	 96.719 (36.0) 172.231 (64.0)	**<0.001**

*: Student's t-test and chi-square test, as appropriate, MAC: Mucinous adenocarcinoma, SD: Standard deviation

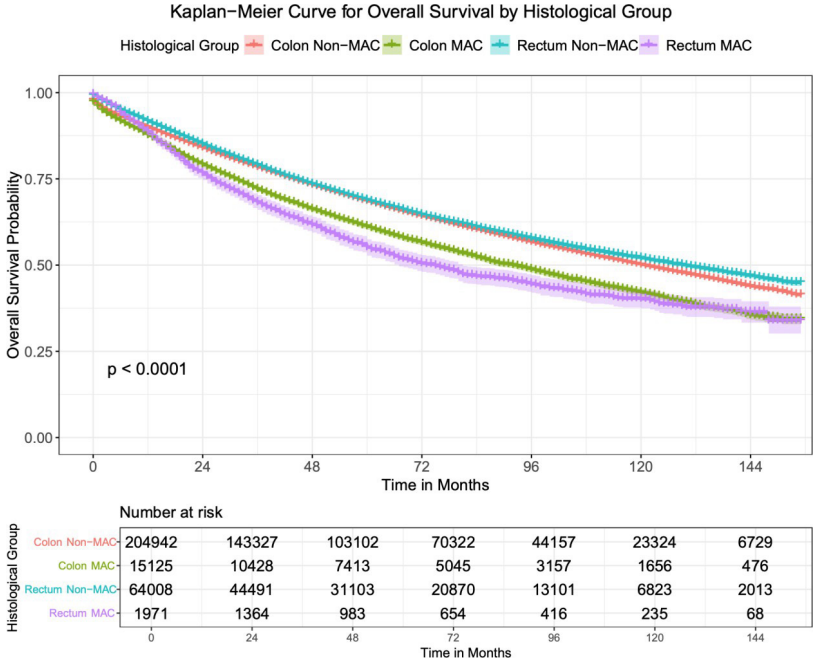

Figure 2. Kaplan-Meier estimates of overall survival stratified by combined tumor location and histology

MAC: Mucinous adenocarcinoma

Table 2. Multivariable Cox regression analysis for overall survival in non-metastatic colorectal cancer

Factor	HR	95% CI	p-value*
Age ≥65 years	2.750	2.710-2.791	**<0.001**
Male sex	1.145	1.130-1.159	**<0.001**
White race	1.044	1.028-1.060	**<0.001**
Stage III (vs. I-II)	1.935	1.905-1.965	**<0.001**
Grade III-IV (vs. I-II)	1.367	1.344-1.391	**<0.001**
Surgery not performed/unknown	3.771	3.691-3.853	**<0.001**
Radiotherapy no/unknown	0.921	0.898-0.945	**<0.001**
Chemotherapy no/unknown	1.754	1.722-1.787	**<0.001**
Rectal cancer (vs. colon)	1.066	1.027-1.106	**0.001**
Mucinous histology (vs. non-mucinous)	1.373	1.326-1.422	**<0.001**
Mucinous histology *x* rectal cancer¥	1.289	1.203-1.381	**<0.001**

*: Cox proportional hazards model, ¥: The significant interaction term (p<0.001) confirms a quantitative effect modification by rectal location on the prognostic impact of mucinous histology, CI: Confidence interval, HR: Hazard ratio

Discussion

The present study, utilizing a large population-based cohort from the SEER database, demonstrates that the prognostic impact of mucinous histology in non-metastatic CRC is significantly modified by the primary tumor location. While MAC was identified as an independent predictor of poor survival overall, our interaction analysis revealed that this adverse effect is disproportionately amplified in rectal tumors than in colonic tumors. These findings challenge the traditional view of MAC as a uniform clinical entity and underscore the necessity of site-specific risk stratification.

Our baseline analysis confirms that MAC exhibits a distinct clinicopathological profile characterized by a predilection for the right colon, female sex, advanced age, and higher tumor grade. These findings align with previous population-based studies (6,7). Consistent with the established literature, we observed that MAC presents with more advanced disease stages at diagnosis (8). Despite adjustment for confounders such as stage, grade, and receipt of treatment, MAC remained an independent adverse prognostic factor. This supports the meta-analysis by Zhang et al. (8), which identified MAC as a risk factor for poor survival even in patients treated with standard adjuvant chemotherapy, and contradicts earlier suggestions that stage correction negates the prognostic significance of mucinous histology (2).

The most critical finding of this study is the statistically significant interaction between histology and tumor site. The survival disadvantage associated with MAC was markedly more pronounced in the rectum (5-year OS: 55.1%) than in the colon (5-year OS: 61.1%); the HR for the interaction term confirmed that mucinous histology had a stronger adverse prognostic effect in rectal than in colonic tumors. This biological heterogeneity is likely driven by differences in treatment response and molecular background. Rectal cancer management relies heavily on neoadjuvant chemoradiotherapy (nCRT) to achieve local control and tumor downstaging. However, a meta-analysis by McCawley et al. (9) demonstrated that rectal MAC is associated with a significantly reduced rate of pathological complete response and tumor downstaging following nCRT, as well as higher rates of positive resection margins. The resistance of mucinous tumors to radiation and fluorouracil-based therapies may partly explain the poorer survival outcomes observed in our rectal MAC cohort (10).

Pharmacogenomic data provide a molecular basis for this chemoresistance. Reynolds et al. (11) identified that MAC harbors distinct somatic mutation profiles, including alterations in *TYMP* and *ATP7B*, which are associated with resistance to 5-fluorouracil and oxaliplatin. Furthermore, clinical studies have consistently shown that MAC patients exhibit poorer response rates to oxaliplatin and irinotecan-based regimens compared to non-mucinous subtypes (12). In the context of colon cancer, where surgery is the primary curative modality and systemic therapy is adjuvant, the impact of chemoresistance might be partially mitigated by adequate surgical resection. Conversely, in the rectum, where multimodality therapy is crucial for R0 resection, this intrinsic resistance likely contributes to the wider survival gap observed in our study.

Another contributing factor to the site-specific prognosis may be differences in the prevalence of MSI. Colonic MAC is frequently associated with MSI-high status, which, despite resistance to 5-fluorouracil, generally confers a more

favorable prognosis and responsiveness to immunotherapy (13,14). Conversely, rectal MAC generally lacks a favorable MSI-high status. Evidence suggests these tumors fall into a distinct molecular class known as consensus molecular subtype 4 (CMS4), the mesenchymal subtype, a biologically aggressive group prone to stromal invasion and poor prognosis (14). Although our dataset lacked specific molecular variables, the observed survival patterns are consistent with this molecular divergence.

The clinical implications of our findings suggest that rectal MAC requires a more aggressive or alternative therapeutic approach. Standard neoadjuvant regimens may be insufficient for this subgroup. Recent evidence suggests that optimizing surgical quality is paramount; Yin et al. (15) proposed that the standard 12-lymph-node harvest might be inadequate for MAC and recommended a threshold of at least 17 nodes to improve prognostic stratification and survival. Additionally, the development of MAC-specific nomograms that incorporate age and stage has shown promise in better predicting cancer-specific survival, allowing for more personalized follow-up and adjuvant strategies (16). For early-onset or stage III cases, despite presumed chemoresistance, systemic therapy remains associated with survival benefits and should not be withheld (17,18).

Study Limitations

This study has several strengths, including the use of a large, nationally representative database and the formal testing of a statistical interaction term. However, limitations exist. First, the SEER database lacks granular data on specific chemotherapy regimens and crucial molecular variables. The absence of data regarding mismatch repair status or MSI status, specific genetic mutations (e.g., KRAS, BRAF), and CMS classification prevents a definitive mechanistic explanation of the observed biological interaction between tumor site and histology.

Second, data regarding patient comorbidities and performance status are unavailable; given the older age of MAC patients, these unmeasured confounders may have influenced OS. Third, because the database does not record tumor recurrence patterns, we could not evaluate disease-free survival or local recurrence rates, which are particularly relevant endpoints in rectal cancer. Furthermore, the SEER classification of radiotherapy and chemotherapy into binary categories ("yes" or "no/unknown") may introduce misclassification bias. Pooling patients with unknown treatment status with genuinely untreated individuals may confound accurate estimation of the effect of these therapies on survival outcomes. Finally, histologic subtyping relied on local pathology reports without central review, potentially introducing inter-observer variability in the the quantitative definition of mucinous histology (>50% mucin content).

Conclusion

Primary tumor location significantly modifies the prognostic impact of mucinous histology in non-metastatic CRC. While mucinous histology is an adverse prognostic factor overall, its negative impact is disproportionately severe in rectal cancer compared to colon cancer. These findings suggest that rectal MAC represents a distinct and particularly aggressive clinical entity, likely driven by intrinsic resistance to standard neoadjuvant therapies and characteristic molecular features. Clinicians should consider mucinous histology and tumor location jointly when determining prognosis. Future research should focus on elucidating the molecular drivers of rectal mucinous tumors to develop targeted therapeutic strategies that overcome their inherent treatment resistance.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. SEER data are publicly available and de-identified; therefore, institutional review board approval was not required.

Informed Consent: Informed consent was not required. Access to the database was granted after signing the SEER data use agreement.

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Footnotes

Authorship Contributions

Surgical and Medical Practises: R.I., Z.A., Concept: R.I., A.O., Z.A., Ö.A., Design: R.I., A.O., Z.A., Ö.A., Data Collection or Processing: R.I., Z.A., Analysis or Interpretation: R.I., A.O., Ö.A., Literature Search: R.I., A.O., Writing: R.I., A.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Reader Questions

Based on the manuscript: "Prognostic Impact of Mucinous Adenocarcinoma According to Primary Tumor Location in Non-metastatic Colorectal Cancer"

1. What was the primary objective of this study?

A. To compare chemotherapy regimens in colorectal cancer

B. To determine whether primary tumor location modifies the prognostic effect of mucinous histology

C. To evaluate immunotherapy outcomes in mucinous colorectal cancer

D. To compare right- and left-sided colon cancer only

Correct Answer: B. To determine whether primary tumor location modifies the prognostic effect of mucinous histology

2. What percentage of the study population had mucinous adenocarcinoma (MAC)?

A. 2%

B. 6%

C. 12%

D. 18%

Correct Answer: B. 6%

3. Which subgroup demonstrated the poorest 5-year overall survival?

A. Colon non-mucinous adenocarcinoma

B. Rectal non-mucinous adenocarcinoma

C. Colon mucinous adenocarcinoma

D. Rectal mucinous adenocarcinoma

Correct Answer: D. Rectal mucinous adenocarcinoma

4. Which statistical approach was used to evaluate whether tumor location modified the prognostic effect of mucinous histology?

A. Propensity score matching

B. Logistic regression

C. Interaction term (histology×location) in a multivariable Cox model

D. Competing-risk analysis

Correct Answer: C. Interaction term (histology×location) in a multivariable Cox model

5. According to the study findings, what was the principal clinical implication?

A. Mucinous histology has no prognostic significance.

B. Colon and rectal mucinous cancers have identical outcomes.

C. Primary tumor location significantly modifies the adverse prognostic impact of mucinous histology.

D. All mucinous colorectal cancers should receive immunotherapy.

Correct Answer: C. Primary tumor location significantly modifies the adverse prognostic impact of mucinous histology.