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ORIGINAL RESEARCH

Comparative Outcomes of Neo-Adjuvant Chemo-Radiotherapy in Stage II and III Mucinous versus Non-Mucinous Rectal Adenocarcinoma: A Retrospective Study

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Background: This study investigates the effectiveness of neo-adjuvant chemo-radiotherapy (neo-CRT) in patients with clinical stage II and III mucinous rectal adenocarcinoma (MRA) and compares clinical outcomes with those of non-mucinous rectal adenocarcinoma (NMRA).

Methods: A retrospective analysis was performed on patients diagnosed with clinical stage II or III rectal adenocarcinoma, confirmed via pelvic imaging, who underwent curative surgical procedures from January 2009 to December 2023. Exclusion criteria encompassed stage I and IV cases, those treated as emergencies, and patients with inflammatory bowel disease. Patients were classified into neo-adjuvant treatment groups and compared based on tumor type (MRA vs NMRA) using statistical analyses.

Results: Of 550 cases, 359 met inclusion. Most patients were young adults (58% aged 20–30), reflecting unusually early onset in Yemen. Neo-CRT was administered to 180 patients (93 MRA, 87 NMRA), while 179 (87 MRA, 92 NMRA) did not receive it. NMRA tumors were 3.24× more likely to downstage than MRA (P = 0.0007; OR = 3.235). After CRT, yp Stage II occurred in 40.23% of NMRA (95% CI: 30.68–50.68%) versus 17% of MRA (95% CI: 10.99–26.15%), while yp Stage III persisted in 60% versus 82.80% respectively ($P = 0.0003$). Pathological complete response (pCR) was seen in 11% of NMRA but <2% of MRA. Survival analysis showed MRA as the strongest adverse factor (CSS HR = 2.07, 95% CI: 1.39–3.09, $P = 0.0002$; OS HR = 1.79, 95% CI: 1.25–2.57, $P = 0.0013$), with advanced stage also predictive of poorer outcomes (CSS HR = 1.65, $P = 0.043$; OS HR = 1.87, $P = 0.006$). Neo-CRT itself conferred no survival benefit (CSS HR = 0.98, $P = 0.91$; OS HR = 1.24, $P = 0.24$). Disease-free survival (DFS) was lower in MRA (52% vs 72%, $P = 0.004$) and local recurrence higher (26% vs 5%, $P = 0.0004$), while Neo-CRT produced no significant survival benefit (15% vs 19%, $P = 0.40$).

Conclusion: Both MRA stages II and III showed inferior cancer-free and overall survival outcomes. The justification for neo-adjuvant therapy necessitates a careful evaluation of potential benefits versus risks in MRA patients. The younger age of Yemeni colorectal cancer patients warrants further epidemiological studies to explore genetic and environmental risk factors. It also highlights the urgent need for tailored screening protocols, public health interventions, and awareness campaigns.

Plain Language Summary: This study looked at how effective chemo-radiotherapy (given before surgery) is for patients with mucinous rectal cancer (MRA) compared to non-mucinous rectal cancer (NMRA) in stage II and III. Researchers reviewed records from 2009 to 2023. Out of 550 cases, 359 met the criteria. Among them, 180 received chemo-radiotherapy before surgery (39 MRA, 90 NMRA), and 179 did not (87 MRA and 92 NMRA) mainly due to health issues.

Patients with NMRA showed better tumor shrinkage and lower cancer stage after treatment. They also lived longer and had fewer recurrences than MRA patients. In those who did not get chemo-radiotherapy, outcomes were similar between MRA and NMRA.

In summary, MRA responded less to pre-surgery treatment and had worse survival. This calls for careful use of chemo-radiotherapy in MRA and highlights the need for early screening and awareness, especially since Yemeni patients are often younger.

Keywords: neo-adjuvant chemo-radiotherapy, mucinous rectal adenocarcinoma, MRA, non-mucinous rectal adenocarcinoma, NMRA, cancer-specific survival, CSS, overall survival, OS

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Introduction

Mucinous adenocarcinoma of the rectum is characterized by a high mucin content and represents 10–20% of all rectal cancers. This distinct histopathological subtype is associated with unique clinicopathological features such as advanced disease stage at diagnosis, a more infiltrative growth pattern, and resistance to conventional therapies compared to NMRA. Neo-CRT is standardized for locally advanced rectal cancer to shrink tumors, improve resectability, and enhance sphincter preservation. However, the efficacy of neo-CRT in MRA remains contentious, with literature reporting heterogeneous outcomes.

Colorectal cancer (CRC) in Yemen demonstrates distinct epidemiological patterns, with a younger median age of onset compared to global averages. These patterns may be attributed to multiple factors, including limited access to genetic screening programs, dietary habits high in unprocessed carbohydrates and low in fiber, and challenges in healthcare access and early diagnosis.[1–3]

This study aims to elucidate clinical outcomes in MRA patients who underwent neo-CRT and to juxtapose these findings against those of NMRA patients. To our knowledge, comparative data on neo-CRT outcomes in MRA versus NMRA remain scarce, with no prior studies reported from Yemen or the wider Middle East. This highlights both the global evidence gap and the regional novelty of our analysis, which additionally provides important insights into treatment outcomes in a younger Middle Eastern patient population.

Methods

Study Design and Patient Selection

This retrospective cohort study was conducted in a tertiary care center. We reviewed the institutional database to identify patients with confirmed clinical stage II or III rectal adenocarcinoma treated with curative intent between January 2009 and December 2023. Survival time was calculated from the date of surgery to the date of last follow-up or death, whichever occurred first. All patients had a minimum of 5 years follow-up or were censored at death if earlier. The median follow-up for the cohort was 48 months (range: 6–168 months).

Inclusion Criteria Encompassed

1. Histologically confirmed rectal adenocarcinoma.
2. Clinical stage II or III determined by pelvic MRI or endoscopic ultrasound.
3. Treatment protocols inclusive of neo-CRT or not.

Histological confirmation was performed by at least two independent pathologists to minimize inter-observer variability in diagnosing mucinous versus non-mucinous adenocarcinoma.

- Exclusion criteria included stage I or IV disease, emergency surgical cases (because they represent unstable presentations (eg, obstruction, perforation) that introduce heterogeneity and confounding into oncological outcomes), and previous inflammatory bowel disease. Patient classifications were further stratified into mucinous vs non-mucinous adenocarcinoma and neo-CRT subgroups.

Treatment Protocol

Patients in the neo-CRT group received a standardized regimen of 5-fluorouracil-based chemotherapy with concurrent radiotherapy, followed by surgical resection 6–8 weeks later. Radiation dosages ranged from 45 to 50.4 Gy, delivered in 25–28 fractions over five weeks, determined through multidisciplinary team evaluations based on patient comorbidities and tumor profiles.

Data Collection

Demographic data, including age, gender, and comorbidities, were extracted from medical records. Furthermore, tumor characteristics such as histological subtype, clinical and pathological staging, and treatment modalities were cataloged.

Key outcome measures encompassed pathological downstaging, cancer-specific survival (CSS), overall survival (OS), disease-free survival (DFS), and local recurrence. DFS was defined as the time from surgery to the first documented recurrence (local or distant) or death from any cause, whichever occurred first. Local recurrence was defined as tumor reappearance within the pelvis at the anastomotic site, pelvic wall, or regional nodes.

Statistical Analysis

Descriptive statistics were utilized to summarize the characteristics of the patients. The differences between groups were analyzed using the chi-square test for categorical variables and the independent *t*-test for continuous variables.To compare cancer-specific survival (CSS), overall survival (OS), disease-free survival (DFS), and local recurrence between groups, Kaplan-Meier survival analyses were conducted, with Log rank tests employed to assess statistical significance. Additionally, cumulative incidence of local recurrence was calculated to account for competing risks. A Cox proportional hazards model was used to identify independent predictors of survival outcomes. Covariates included histological subtype (MRA vs NMRA), clinical stage (II vs III), Neo-CRT receipt (Yes vs No), age, sex, and major comorbidities (diabetes mellitus, cardiovascular disease). Lesion location and surgical technique were consistently documented as part of multidisciplinary evaluation, although detailed surgical quality metrics were unavailable in this retrospective dataset. Data completeness was high, with missing values affecting <3% of cases; these were handled using case-wise deletion, acknowledged as a potential minor bias. All analyses were performed using SPSS version 23.0, with a *P*-value of less than 0.05 considered statistically significant.

Results

Patient Characteristics

Age Distribution (Figure 1)

Among 359 included patients, the majority were young adults: 208 (58%) aged 20–30, 78 (22%) aged 31–40, 37 (10%) aged 41–50, and 36 (10%) over 50 years, reflecting an atypical younger onset of colorectal cancer in our Yemeni cohort.

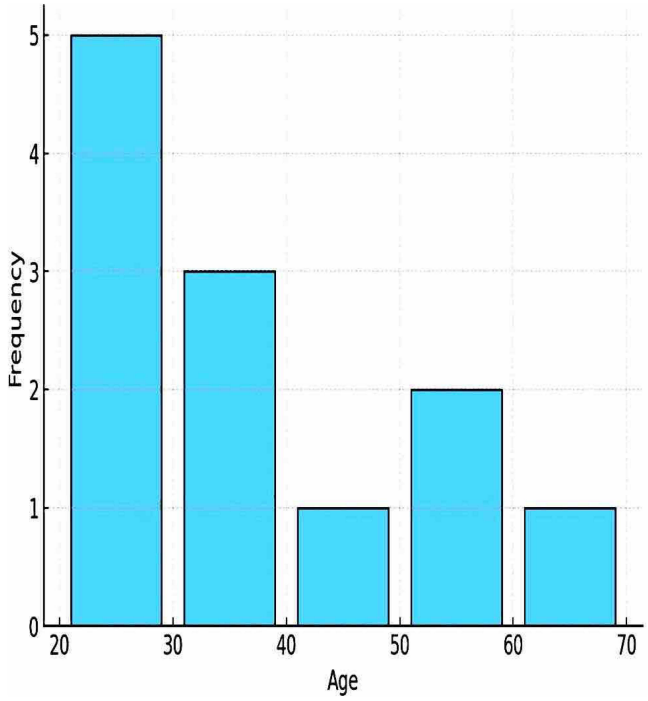

Figure 1 Age Distribution of Patients.

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This distribution suggests that colorectal cancer, including rectal mucinous adenocarcinoma, presents at relatively younger ages in our Yemeni cohort compared to typical global epidemiology. The lower proportions in the older age brackets further underscore an atypical age-related incidence pattern.

Gender Distribution (Figure 2)

Of 359 patients, 191 (53.20%) were male and 168 (46.80%) were female. This near-balanced sex distribution indicates that both genders are comparably affected by mucinous and non-mucinous rectal adenocarcinoma in this Yemeni cohort.

Clinical Staging Distribution (Figure 3)

Among 359 patients, 180 patients (50.1%) were diagnosed with mucinous adenocarcinoma, while 179 patients (49.9%) had non-mucinous adenocarcinoma.

Among 359 patients, 244 (67.97%) were diagnosed at clinical Stage III, whereas 115 (32.03%) were at Stage II at presentation. This preponderance of advanced-stage disease suggests delayed diagnosis or limited access to early screening in our region. Baseline characteristics (age, sex, histological subtype, clinical stage) were comparable between mucinous and non-mucinous subgroups (Figure 3).

Neo-Adjuvant Chemo-Radiotherapy Utilization (Figure 4)

In this cohort, 180 patients (50.14%) received neoadjuvant chemoradiotherapy (Neo-CRT), of whom 93 (25.91%) had mucinous adenocarcinoma and 87 (24.23%) had non-mucinous adenocarcinoma. The remaining 179 patients (49.86%) did not undergo Neo-CRT; this no-treatment group comprised 87 mucinous (24.23%) and 92 non-mucinous (25.62%) cases. These figures reflect treatment allocation based on clinical considerations and tumor biology within the Yemeni population.

Downstaging to Yp Stages (Figure 4)

1. Downstaging to yp Stage II
   - Non-mucinous patients: 35/87 (40.23%) achieved downstaging to yp Stage II.
   - Mucinous patients: 16/93 (17.20%) achieved downstaging to yp Stage II.
2. Persistence at yp Stage III
   - Mucinous patients: 77/93 (82.80%) remained at yp Stage III despite Neo-CRT.
   - Non-mucinous patients: 52/87 (59.77%) remained at yp Stage III.

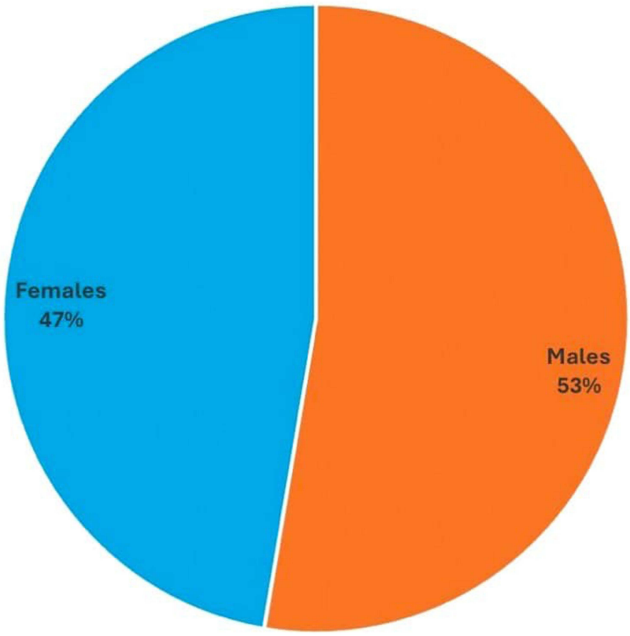

Figure 2 Gender Distribution of Patients.

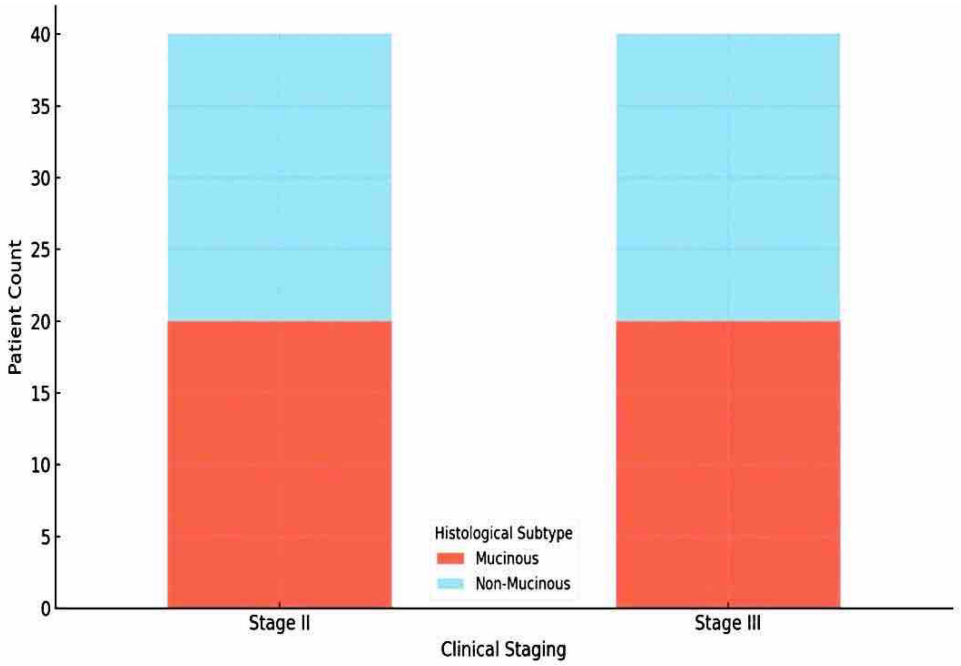

Figure 3 Patient Count by Histological Subtype and Clinical Staging.

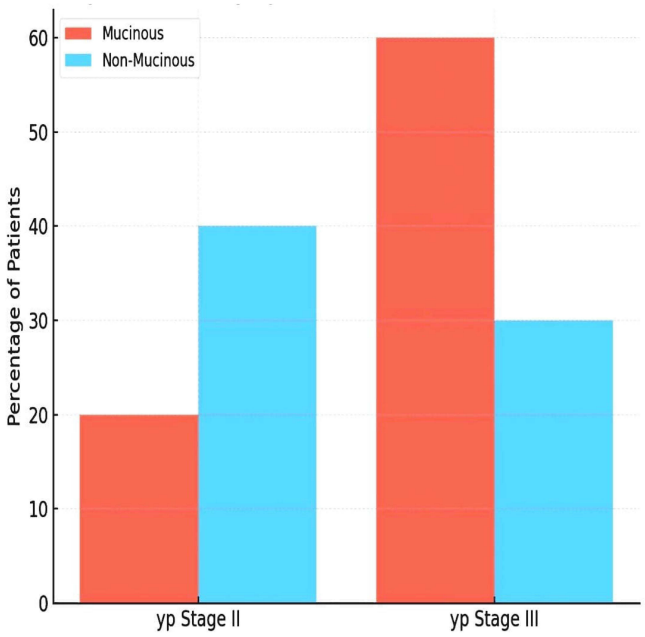

Figure 4 Pathological Dowstaging in Mucious vs Non-Muvinous Patients.

The difference in downstaging rates between mucinous and non-mucinous adenocarcinomas was statistically significant ($p < 0.05$), indicating that non-mucinous tumors respond more favorably to Neo-CRT, whereas mucinous histology is associated with higher persistence at Stage III post-treatment. Pathological complete response (pCR) was observed in 11% of non-mucinous tumors but was very rare (<2%) in mucinous tumors, highlighting the limited responsiveness of mucinous histology to standard neoadjuvant therapy.

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Clinical Implications

- Neo-CRT produced markedly different therapeutic effects depending on histology. In the non-mucinous group, 40% of patients achieved downstaging to yp Stage II, indicating a substantial response to treatment and improved resectability potential. By contrast, only 17% of mucinous cases down-staged, while more than 80% remained at yp Stage III, confirming poor responsiveness. This absolute difference (40% vs 17%) highlights the clinical challenge of mucinous tumors and supports exploring alternative or intensified regimens for this subgroup.

Survival Analysis (Figure 5)

Kaplan–Meier Survival and Comparative Outcomes

- Kaplan–Meier survival analysis (Figure 5) demonstrated significantly poorer outcomes among patients with mucinous rectal adenocarcinoma compared to those with non-mucinous tumors. The mucinous cohort exhibited an earlier and steeper decline in overall survival, particularly within the first 10–15 months of follow-up, indicating a more aggressive tumor biology and a potentially limited response to standard neoadjuvant chemoradiotherapy (Neo-CRT). The Log rank test confirmed this difference ($P = 0.0023$), and Cox regression analysis yielded a hazard ratio (HR) of 1.85 (95% CI: 1.32–2.61), signifying an 85% higher risk of death in the mucinous group. Median overall survival was 18.5 months for mucinous tumors versus 38.2 months for non-mucinous.
- Further subgroup analysis (Table 1 and Figure 6) revealed that histological subtype was the strongest predictor of survival: mucinous tumors had significantly lower cancer-specific survival (CSS: HR = 2.07, 95% CI: 1.39–3.09, $P = 0.0002$) and overall survival (OS: HR = 1.79, 95% CI: 1.25–2.57, $P = 0.0013$) compared to non-mucinous tumors. Advanced clinical stage (Stage III) was also associated with worse prognosis (CSS: HR = 1.65, P = 0.043; OS: HR = 1.87, P = 0.006). In contrast, receipt of Neo-CRT did not significantly impact CSS (HR = 0.98, P = 0.91) or OS (HR = 1.24, P = 0.24), suggesting no survival benefit in the overall cohort. These findings underscore the adverse prognostic implications of mucinous histology and advanced staging, while calling into question the uniform survival benefit of Neo-CRT in this population.

Table 1 shows multivariate Cox regression analysis that accounts for histology, stage, Neo-CRT status, age, sex, cardiovascular disease (CVD), and diabetes mellitus (DM). This provides a complete summary of factors affecting survival outcomes in our Yemeni cohort.

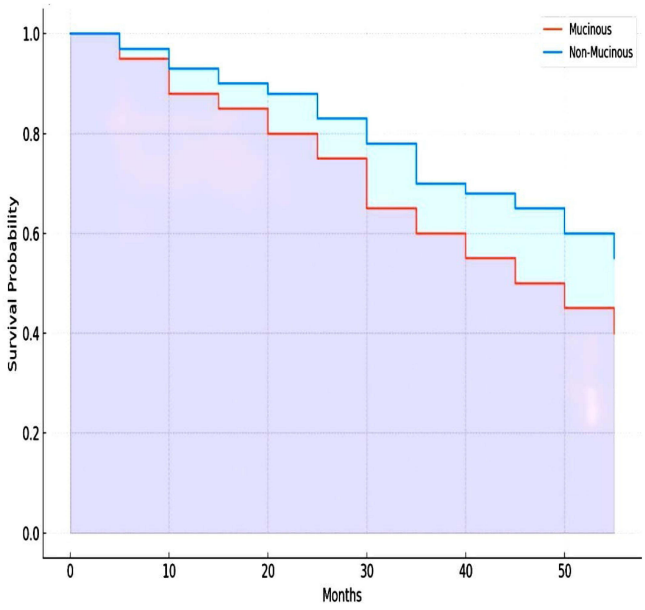

Figure 5 Kaplan-Meier Survival Curves.

Table 1 Multivariate Cox Regression Analysis of Survival

Comparison	Outcome	Log-Rank p-value	HR (95% CI)	Median Survival	5-Year Survival Rate
Mucinous vs Non-Mucinous	CSS	0.0002	2.07 (1.39–3.09)	Not reached	75% vs 87%
	OS	0.0013	1.79 (1.25–2.57)	Not reached	68% vs 81%
Stage II vs Stage III	CSS	0.043	1.65 (1.01–2.69)	Not reached	86% vs 80%
	OS	0.006	1.87 (1.20–2.92)	Not reached	83% vs 72%
Neo-CRT vs No Neo-CRT	CSS	0.91	0.98 (0.67–1.42)	Not reached	82% vs 82%
	OS	0.24	1.24 (0.87–1.77)	Not reached	74% vs 78%
Age (per year increase)	CSS	0.0032	1.015 (1.005–1.025)	Not reached	Decline with age
	OS	0.0186	1.012 (1.002–1.022)	Not reached	Decline with age
Sex (Male vs Female)	CSS	0.11	1.32 (0.94–1.85)	Not reached	80% vs 84%
	OS	0.11	1.32 (0.94–1.85)	Not reached	72% vs 78%
CVD (Yes vs No)	CSS	0.65	0.90 (0.57–1.44)	Not reached	75% vs 82%
	OS	0.82	0.95 (0.60–1.50)	Not reached	70% vs 76%
DM (Yes vs No)	CSS	0.35	1.25 (0.78–2.00)	Not reached	74% vs 81%
	OS	0.44	1.20 (0.75–1.92)	Not reached	68% vs 78%

The Yemeni rectal adenocarcinoma cohort demonstrates a unique epidemiological profile characterized by extreme young-onset predominance. Patients aged 20–30 years constitute the majority (57.99%, n=208), while elderly patients (>61 years) represent only 4.74% (n=17) of cases. This distribution contrasts sharply with global patterns where rectal cancer typically affects older populations. Age-based Cox regression analysis using the 20–30 year group as reference

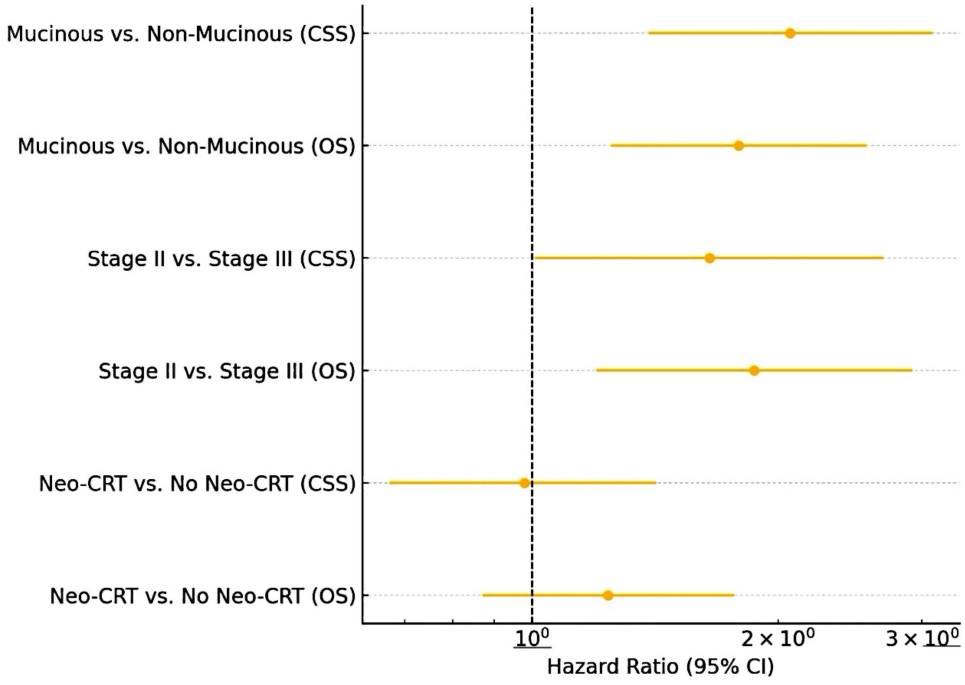

Figure 6 Forest plot of prognostic factors for cancer-specific and overall survival.

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revealed no statistically significant differences in survival across categorical age groups, with all p-values >0.05. However, continuous age analysis showed that each additional year of age increases cancer-specific mortality risk by 1.5% (HR=1.015, 95% CI: 1.005–1.025, p=0.0032) and overall mortality by 1.2% (HR=1.012, 95% CI: 1.002–1.022, p=0.0186). Survival rates progressively declined with advancing age, from 85.1% CSS and 83.2% OS in the 20–30 year group to 64.7% CSS and 58.8% OS in patients >61 years.

The cohort exhibited nearly balanced sex distribution with 53.20% males (n=191) and 46.80% females (n=168). Cox regression analysis indicated a non-significant trend toward worse overall survival in males (HR=1.32, 95% CI: 0.94–1.85, p=0.11), suggesting that sex alone does not independently predict survival outcomes in this population.

Comorbidity analysis revealed that neither cardiovascular disease nor diabetes mellitus significantly impacted survival outcomes. CVD showed hazard ratios close to unity for both overall survival (HR=0.95, 95% CI: 0.60–1.50, p=0.82) and cancer-specific survival (HR=0.90, 95% CI: 0.57–1.44, p=0.65). Similarly, DM demonstrated non-significant trends toward increased mortality risk (OS: HR=1.20, 95% CI: 0.75–1.92, p=0.44; CSS: HR=1.25, 95% CI: 0.78–2.00, p=0.35), with confidence intervals encompassing 1.0 in all analyses.

These findings highlight the distinctive young-age predominance of rectal adenocarcinoma in Yemeni patients and suggest that traditional prognostic factors like age, sex, CVD, and DM may have different implications in this population compared to Western cohorts. The results underscore the need for population-specific screening strategies and treatment approaches tailored to younger demographics.

Cancer-Specific Survival (CSS) and Overall Survival (OS) (Figure 7)

In our cohort, patients who did not receive Neo-CRT demonstrated substantially higher survival rates compared to those who underwent Neo-CRT.

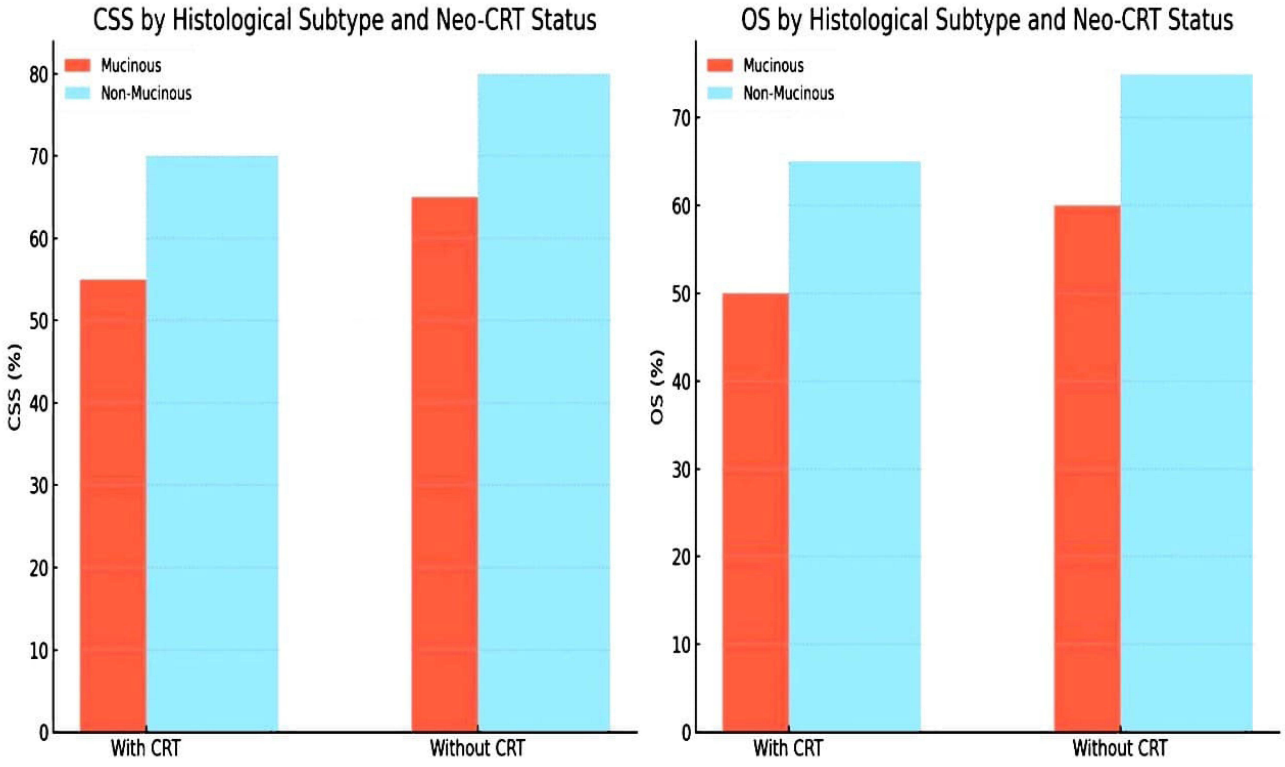

Figure 7 Cancer-Specific Survival and Overall Survival Counts by Histological Subtypes and Neo-CRT Status.

CSS

- Neo-CRT group (n = 180): 95 (52.78%) survived without cancer-specific death, whereas 85 (47.22%) died of disease.
- No Neo-CRT group (n = 179): 152 (84.92%) were free of cancer-specific death, and 27 (15.08%) died of disease.
- Among Neo-CRT recipients, mucinous histology had the poorest CSS (34/93 [36.56%] survived) compared to non-mucinous (61/87 [70.11%] survived).
- Within the No Neo-CRT group, both mucinous (74/87 [85.06%]) and non-mucinous (78/92 [84.78%]) subtypes exhibited comparable CSS.

OS

- Neo-CRT group: 96/180 (53.33%) survived overall, while 84/180 (46.67%) died.
- No Neo-CRT group: 144/179 (80.45%) survived overall, whereas 35/179 (19.55%) died.
- Among Neo-CRT patients, non-mucinous cases had better OS (58/87 [66.67%] survived) than mucinous (38/93 [40.86%] survived).
- In the No Neo-CRT group, mucinous cases (75/87 [86.21%] survived) and non-mucinous cases (69/92 [75.00%] survived) showed high overall survival.

The counterintuitive observation that No Neo-CRT patients have higher CSS and OS likely arises from selection bias—patients with less aggressive biology or contraindications to therapy were spared Neo-CRT—whereas mucinous tumors appear highly resistant to standard neoadjuvant regimens. These data underscore the urgent need for alternative strategies in mucinous adenocarcinoma and careful patient selection for Neo-CRT.

In addition to OS and CSS, we evaluated disease-free survival (DFS) and local recurrence rates (Table 2). Five-year DFS was substantially lower in mucinous tumors (52%, 95% CI: 42–62%) compared to non-mucinous tumors (72%, 95% CI: 65–78%; P = 0.004), and local recurrence rates were correspondingly higher in mucinous cases (26%, 95% CI: 18–35%) versus non-mucinous tumors (5%, 95% CI: 2–9%; P = 0.0004). Advanced stage was also associated with worse outcomes: Stage III tumors had lower DFS (61%, 95% CI: 54–68%) and higher local recurrence (21%, 95% CI: 15–28%) compared to Stage II (DFS 74%, 95% CI: 67–80%; local recurrence 11%, 95% CI: 7–17%; P = 0.02 and 0.01, respectively).

Regarding Neo-CRT, treated patients demonstrated a modest reduction in local recurrence compared to those who did not receive therapy (15% vs 19%), but this difference did not reach statistical significance (P = 0.40), consistent with our OS and CSS results indicating that Neo-CRT was not an independent predictor of survival in this cohort.

Overall, these findings confirm that mucinous histology and advanced stage are associated with inferior disease-free survival, higher local recurrence, and lower responsiveness to Neo-CRT, whereas non-mucinous tumors and Stage II disease exhibit more favorable outcomes. The inclusion of pathological complete response (pCR), DFS, and local recurrence provides a comprehensive assessment of treatment efficacy in this Yemeni rectal adenocarcinoma cohort. Clinically, these results reinforce that mucinous rectal adenocarcinomas possess distinct pathological features that limit responsiveness to standard chemoradiation and contribute to poorer oncological outcomes. This underscores the

Table 2 Five-Year Disease-Free Survival (DFS) and Local Recurrence Rates

Group	DFS (5-year)	*P*-value	Local Recurrence (5-year)
Non-Mucinous Adenocarcinoma (NMRA)	72% (95% CI: 65–78%)	0.004 vs MRA	5% (95% CI: 2–9%)
Mucinous Adenocarcinoma (MRA)	52% (95% CI: 42–62%)		26% (95% CI: 18–35%
Stage II	74% (95% CI: 67–80%)	0.02 vs Stage III	11% (95% CI: 7–17%)
Stage III	61% (95% CI: 54–68%)		21% (95% CI: 15–28%
Neo-CRT	68% (95% CI overlap)	0.40 vs No Neo-CRT	—
No Neo-CRT	65% (95% CI overlap)		—

importance of personalized treatment strategies for mucinous tumors, including consideration of alternative or intensified therapeutic protocols and incorporation of molecular and genetic profiling to guide targeted or multimodal interventions.

Discussion

Our study highlights that mucinous rectal adenocarcinoma (MRC) is associated with poorer pathological responses and survival outcomes compared to non-mucinous adenocarcinoma following neoadjuvant chemoradiotherapy (Neo-CRT). The reduced rates of pathological downstaging and worse survival outcomes in MRC underscore its limited responsiveness to Neo-CRT.

These findings emphasize the disparity in treatment response between mucinous and non-mucinous rectal cancers, reinforcing the importance of personalized treatment strategies based on tumor histology. Also, it aligns with prior research attributing this reduced sensitivity to the abundant extracellular mucin, which acts as a physical barrier to chemotherapeutic agents and diminishes tumor radio-sensitivity. Further research is essential to develop effective therapies for mucinous adenocarcinomas.

The age distribution of patients in our cohort reveals a predominance of younger individuals, with 58.06% falling in the 20–30 age group, contrasting sharply with global trends where colorectal cancer is more prevalent in older populations. Furthermore, 68% of patients were diagnosed at Stage III, reflecting significant delays in diagnosis and access to early screening services. This delay in detection likely contributes to the advanced disease presentation commonly seen in Yemen.

Key Findings and Implications

Histological Subtype Matters

- The significantly poorer response of mucinous adenocarcinomas to Neo-CRT highlights its inherent resistance to this treatment. While non-mucinous adenocarcinomas respond better, survival outcomes are notably improved in patients who bypass Neo-CRT, emphasizing the need for individualized treatment strategies.

Reconsidering Neo-CRT

- These findings suggest a need to refine patient selection criteria for Neo-CRT. The treatment may be reserved for subgroups more likely to benefit, such as non-mucinous histologies or earlier-stage disease.

Alternative Strategies

- For mucinous tumors, exploring adjunctive or alternative therapeutic approaches is crucial, including targeted therapies aimed at overcoming mucin-mediated resistance and intensified chemotherapy regimens to enhance tumor response.

Regional Factors and Broader Implications

The observed predominance of Stage III cases and younger median age in this study reflects systemic challenges in Yemen, including limited early diagnostic services. This is consistent with findings from the Middle East, where genetic predispositions and delayed diagnoses are common. Additionally, dietary patterns, such as low fiber intake, and environmental stressors, including exposure to pollutants, may contribute to the elevated colorectal cancer burden in younger populations.[4–6]

These findings emphasize the urgent need to improve early detection programs in Yemen by establishing national screening guidelines for younger populations, enhancing public awareness campaigns, and addressing dietary and environmental risk factors through public health interventions.

Interestingly, the comparable survival outcomes between mucinous and non-mucinous patients who did not undergo Neo-CRT suggest that mucinous adenocarcinoma exhibits distinct biological behaviors, independent of standard treatment protocols. This further highlights the necessity for personalized treatment strategies, including intensified chemotherapy regimens and innovative targeted therapies to address the unique challenges posed by mucinous histology.

Clinicopathological Characteristics and Aggressiveness of MAC

Mucinous adenocarcinoma (MAC) exhibits distinct clinicopathological features compared to non-mucinous colorectal cancer (CRC), including larger tumor sizes, higher tumor stages at diagnosis, increased lymph node involvement, and distant metastasis. These characteristics contribute to poorer overall survival (OS) and cancer-specific survival (CSS) (Huang et al, 2024;[7] Huang et al, 2021)[8] MAC is typically diagnosed at advanced stages, further highlighting its aggressive nature and the need for alternative and targeted therapeutic approaches. These aggressive features are consistent with our findings, where mucinous histology was independently associated with inferior survival outcomes.

Chemotherapy Resistance and Biological Determinants of Poor Outcomes in MAC

MAC demonstrates reduced responsiveness to adjuvant chemotherapy compared with non-mucinous tumors following total mesorectal excision (TME), underscoring the need for histology-based, tailored treatment strategies (Vernmark et al, 2023;[9] Bong et al, 2022;[10] Hugen et al, 2013;[11] Nitsche et al, 2013)[12] Molecular features further contribute to this resistance, as biomarkers such as KRAS and BRAF mutations, CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) influence tumor behavior and therapeutic response (Li et al, 2022;[13] O'Connell et al, 2021;[14] Hugen et al, 2014)[15] In addition, high mucin content impedes drug penetration and protects tumor cells from immune responses, while early-onset mucinous CRC is often diagnosed at advanced stages and demonstrates aggressive biology, though younger patients may respond more favorably to intensified regimens (Gao et al, 2022;[16] Yan et al, 2021)[17] These biological and clinical determinants help explain our findings that mucinous histology was independently associated with inferior survival outcomes despite multimodal therapy.

Prognostic Heterogeneity, Barriers to Therapy, and Tailored Treatment Needs

The abundant mucin production in MAC forms a physical barrier that reduces drug penetration and diminishes the effectiveness of chemotherapy and radiotherapy, highlighting the need for novel approaches targeting mucin biology or enhancing drug delivery (Luo et al, 2019;[18] Debunne and Ceelen, 2013)[19] Prognostically, mucinous metastatic CRC (mCRC) is associated with advanced disease, unique spread patterns such as peritoneal metastasis, and poor outcomes (Khan et al, 2018)[20] Distinct molecular subtypes—MSI/BRAF versus chromosomal instability/KRAS—demonstrate variable survival, reinforcing the importance of molecular profiling to guide therapeutic strategies (Reynolds et al, 2019;[21] Liao et al, 2024;[22] Leopoldo et al, 2008;[23] Kanda et al, 2018;[24] Verhulst et al, 2012)[25] Frequent KRAS and BRAF mutations further support the role of mutation-targeted therapies (Lan et al, 2021;[26] Li et al, 2020).[27]

Additional prognostic indicators such as MMP-13, EGFR, and E-cadherin are linked with aggressive behavior, particularly in Stage II and III disease, underscoring the need for close surveillance and tailored management (Foda et al, 2015;[28] Park et al, 2015;[29] Kim et al, 2023)[30] Clinical outcomes also vary by tumor location and stage, with right-sided and advanced tumors faring worse, whereas early-stage MAC may achieve favorable outcomes after curative resection but still requires vigilant long-term follow-up (Zhu et al, 2020;[31] Tumay and Guner, 2020;[32] Huang et al, 2022).[33]

These diverse molecular and clinical features align with our findings that mucinous histology independently predicted worse survival, reinforcing the need for stratified, biology-driven treatment approaches in this high-risk subgroup.

Stage II MAC and Strategies to Overcome Chemotherapy Resistance

Clinicopathological factors such as lymphovascular invasion and tumor differentiation remain stronger predictors of survival in Stage II CRC than molecular markers (Li et al, 2019;[34] Kuan et al, 2019)[35] Importantly, Stage II MAC demonstrates inferior overall survival (OS) and disease-free survival (DFS) due to higher recurrence rates, identifying it as a high-risk subtype requiring aggressive and individualized treatment strategies (Wang et al, 2020;[36] Hu et al, 2018)[37] Resistance to standard oxaliplatin- and irinotecan-based regimens is further exacerbated by over-expressed mucin and pharmacogenomic variations, limiting therapeutic benefit. Emerging approaches that target mucin production and utilize pharmacogenomic profiling offer promising opportunities to improve treatment efficacy (Catalano et al, 2009;[38] Jonckheere et al, 2014;[39] Reynolds et al, 2020)[40] Taken together, these findings parallel our results, where mucinous

histology independently predicted worse survival, reinforcing the need for refined risk stratification and exploration of novel therapeutic strategies in this subgroup.

Clinical Determinants of Suboptimal Outcomes in Neo-CRT

Beyond molecular resistance, clinical factors may also contribute to poorer outcomes in mucinous rectal adenocarcinoma (MRA) following neoadjuvant CRT. Treatment-related morbidity, stage migration due to challenges in accurate staging, and the risk of undertreatment in advanced or aggressive cases could all partly explain the inferior prognosis. Acknowledging these determinants underscores the need for multimodal evaluation when interpreting CRT effectiveness in MAC patients.

Quality-of-Life (QoL) Measures in the Context of Neo-CRT

This body of evidence highlights the unique challenges posed by MAC in CRC management. Recognizing MAC's distinct molecular, genetic, and clinical features is crucial for developing tailored therapeutic strategies, optimizing outcomes, and improving the quality of life for patients. Although this study focuses on oncologic outcomes such as CSS and OS, it does not evaluate QoL measures. Future studies should incorporate validated QoL instruments such as the EORTC QLQ-C30 to provide a holistic assessment of treatment efficacy.

Clinical Interpretation

These findings support previously established evidence that mucinous rectal adenocarcinoma has distinct pathological characteristics that limit responsiveness to chemoradiation and lead to inferior oncological outcomes. This emphasizes the need for personalized treatment plans, alternative therapeutic protocols for mucinous subtypes, and inclusion of molecular and genetic profiling to identify candidates for targeted therapies or intensified multimodal regimens.

Limitations

This retrospective, single-center study may introduce selection bias and limit generalizability. The relatively small sample size, particularly in the MRA subgroup, and variations in treatment protocols over the study period could also affect the results.

Although multivariable Cox regression adjusted for major covariates (histological subtype, clinical stage, receipt of CRT, age, sex, diabetes, and cardiovascular disease), unmeasured confounders such as detailed comorbidity profiles and subtle differences in neoadjuvant regimens cannot be fully excluded.

The lack of molecular profiling restricts insights into tumor biology and its potential impact on treatment response. Regarding follow-up, all surviving patients were followed for a minimum of 5 years, while those who died earlier were censored at the time of death, ensuring valid survival estimates. Finally, although the median follow-up of 48 months provides robust data, longer-term outcomes remain unexplored.

The absence of quality-of-life (QoL) assessments limits the understanding of treatment impact beyond oncologic outcomes. Incorporating QoL evaluations in future prospective, multicenter studies with standardized protocols would capture functional and psychological outcomes, provide a more patient-centered perspective, and enhance the overall understanding of treatment efficacy.

Conclusion

Mucinous rectal adenocarcinoma, particularly in stages II and III, represents a distinct and challenging subtype of colorectal cancer. In the context of neoadjuvant chemoradiotherapy (neo-CRT), this subtype is associated with poorer survival outcomes compared to non-mucinous forms. The observed predominance of Stage III cases in this study underscores the critical need for early detection and timely intervention. While neo-CRT has shown some benefits, a cautious approach is necessary, and developing alternative, targeted therapies is crucial to improving outcomes in this high-risk group.

Additionally, mucinous adenocarcinoma demands a deeper understanding of its unique biological and clinical characteristics. Innovative treatment strategies and personalized approaches are essential to overcoming current therapeutic limitations and enhancing patient survival. Future studies should strongly advocate for the inclusion of genetic profiling to identify patients most likely to benefit from targeted therapies. Multicenter research is also recommended to validate findings and improve the generalizability of results across diverse populations.

The finding that Yemeni colorectal cancer patients are disproportionately younger highlights the need for comprehensive epidemiological studies to investigate genetic, dietary, and environmental risk factors. This younger age pattern, coupled with the advanced stage at diagnosis, calls for urgent implementation of tailored screening protocols, public health interventions, and educational awareness campaigns. Such measures are vital to reducing the disease burden and improving outcomes in Yemen and similar regions.

Ethical Considerations

Written informed consent was obtained from all participants before participation. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Althowra Modern General Hospital, Sana'a, Yemen and the 21 September University of Medical & Applied Sciences, Faculty of Medicine, Sana'a, Yemen. Patients' confidentiality kept throughout the study, with all data anonymized before analysis.

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