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Prognostic Impact of Tumor Regression and Downstaging After Neoadjuvant Therapy in Rectal Cancer

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ABSTRACT

Background & Objective: Rectal cancer is a common malignancy associated with substantial morbidity. Neoadjuvant chemoradiotherapy (CRT) is the standard treatment for locally advanced disease, often resulting in tumor regression and downstaging. This study aimed to evaluate the relationship between these response patterns and patient prognosis.

Methods: A retrospective cohort study was conducted on 200 rectal cancer patients treated with neoadjuvant therapy between 2022 and 2024 at a private pathology laboratory in Isfahan, Iran. Tumor regression was graded using the Dworak system, and downstaging was assessed according to AJCC/UICC-TNM criteria. Patients were followed to evaluate associations with mortality and three-year disease-free survival (DFS).

Results: Neither downstaging nor tumor regression significantly predicted disease-free survival in linear models, with downstaging showing $F = 0.828$ ($p = 0.364$) and regression yielding $R^2 = 0.001$ ($p = 0.658$). However, logistic regression analysis demonstrated that tumor regression significantly predicted mortality ($B = 0.568$, $p = 0.046$, $Exp(B) = 1.765$), whereas downstaging was not significant ($B = -0.290$, $p = 0.600$). The model explained 2.2%–4.5% of the variance in mortality and showed acceptable fit (Hosmer–Lemeshow $\chi^2 = 3.418$, $p = 0.491$).

Conclusion: Tumor biology and lymph node involvement appear to be stronger predictors of prognosis than regression or downstaging alone. Neither parameter significantly predicted disease-free survival. However, tumor regression was significantly associated with mortality, whereas downstaging was not.

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Introduction

Rectal cancer is a prevalent and potentially fatal disease worldwide. In 2025, approximately 46,950 new cases are expected in the United States, including 27,950 in men and 19,000 in women (1). Neoadjuvant chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer (2), resulting in tumor downstaging and pathological complete response (pCR) in approximately 15–42% of patients following total mesorectal excision (TME) (3).

Preoperative radiochemotherapy has been shown to reduce the risk of local recurrence compared with postoperative treatment in advanced rectal cancer (4). Tumor regression and downstaging are considered important prognostic indicators. Patients who achieve downstaging to lower pathological stages often demonstrate long-term outcomes comparable to those initially diagnosed with early-stage disease. Furthermore, pathological response to neoadjuvant therapy has been proposed as a predictor of oncologic outcomes in locally advanced rectal cancer (5).

Understanding the differences between response patterns—tumor regression versus downstaging—may help explain variations in recurrence risk and residual disease. Early identification of high-risk patients may improve outcomes and enable tailored therapeutic strategies. Therefore, this study aimed to evaluate the relationship between pathological response patterns and patient prognosis.

Materials and Methods

This retrospective cohort study included 200 patients diagnosed with rectal carcinoma who underwent neoadjuvant therapy between 2022 and 2024 in a private pathology laboratory in Isfahan, Iran. Inclusion criteria comprised patients with available treatment response data and adequate follow-up for outcome assessment. Patients without sufficient follow-up information were excluded.

Tumor regression and downstaging were evaluated in all eligible cases. Prognosis and three-year disease-free survival were analyzed in relation to age, treatment modality, and other clinical factors. Tumor regression was graded according to the Dworak system (6): Grade 0, no regression; Grade 1, dominant tumor mass with fibrosis or vasculopathy; Grade 2, predominantly fibrotic changes with few tumor cells; and Grade 3, complete regression with no viable tumor cells. Downstaging was assessed using the AJCC/UICC-TNM classification system (7).

Follow-up data, including recurrence status, were obtained through direct contact with patients or their companions.

Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize data. Associations between categorical variables were evaluated using Pearson's Chi-square test, Fisher's exact test, or the likelihood ratio test, as appropriate. Normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Depending on data distribution, parametric (independent t-test, one-way ANOVA) or non-parametric (Mann–Whitney U test, Kruskal–Wallis test) methods were applied. A P-value < 0.05 was considered statistically significant.

Results

A total of 200 patients were evaluated in this study. The mean age was 60.6 ± 11.9 years. Among the study population, 79 patients (39.5%) demonstrated downstaging following neoadjuvant therapy. The distribution of tumor regression grades (Dworak 0–3) was as follows: 36 cases (18.0%) with grade 0, 43 cases (21.5%) with grade 1, 79 cases (39.5%) with grade 2, and 42 cases (21.0%) with grade 3.

The overall mortality rate was 10.5% (21 patients) (Table 1). Tumor type and degree of differentiation showed a clear association with mortality, supporting the concept that intrinsic tumor biology is a major determinant of outcome following neoadjuvant therapy.

The presence of tertiary lymphoid structures (TLS) demonstrated a statistically significant association with mortality in univariable analysis; however, this finding should be interpreted with caution. Previous studies have more consistently associated TLS with improved response to chemoradiotherapy (CRT) rather than with adverse outcomes. Moreover, the present study was not sufficiently powered to establish an independent prognostic role for TLS.

Table 1. Comparing study variables with mortality status

Variable	Status	Mortality		P value
		No (n=179)	Yes (n=21)	
Age (Year, Mean ± SD)		60.7 ± 11.8	60.0 ± 13.4	0.228*
Downstaging	Positive	72 (91.1%)	7 (8.9%)	0.641¶
	Negative	107 (88.4%)	14 (11.6%)	
Regression score	3	33 (91.7%)	3 (8.3%)	0.078¶
	2	42 (97.7%)	1 (2.3%)	
	1	70 (88.6%)	9 (11.4%)	
	0	34 (81.0%)	8 (19.0%)	
Tumor type	Poorly differentiated adenocarcinoma	10 (83.3%)	2 (16.7%)	0.005¶
	Moderately differentiated adenocarcinoma	6 (66.7%)	3 (33.3%)	
	Well differentiated adenocarcinoma	159 (91.9%)	14 (8.1%)	
	SCC	0 (0%)	2 (100%)	
	Signet Cell	2 (100%)	0 (0%)	
	Mucinous	2 (100%)	0 (0%)	
Treatment	Chemotherapyalone	11 (78.6%)	3 (21.4%)	0.307¶
	Radiotherapyalone	7 (100%)	0 (0%)	
	Chemoradiotherapy	161 (89.9%)	18 (10.1%)	
Tertiary lymph node	No	115 (93.5%)	8 (6.5%)	0.031¶
	Yes	64 (83.1%)	13 (16.9%)	

Table 2. Comparing study variables based on tumor downstaging status

Variable	Status	Downstaging		P value
		Positive (n=79)	Negative (n=121)	
Age (Year, Mean ± SD)		59.7 ± 10.8	61.2 ± 12.6	0.403*
Tumor type	Poorly differentiated adenocarcinoma	0 (0%)	12 (100%)	0.001¶
	Moderately differentiated adenocarcinoma	1 (11.1%)	8 (88.9%)	
	Well differentiated adenocarcinoma	78 (45.1%)	95 (54.9%)	
	SCC	0 (0%)	2 (100%)	
	Signet Cell	0 (0%)	2 (100%)	
	Mucinous	0 (0%)	2 (100%)	
Treatment	Chemotherapyalone	4 (28.6%)	10 (71.4%)	0.500¶
	Radiotherapyalone	4 (57.1%)	3 (42.9%)	
	Chemoradiotherapy	71 (39.7%)	108 (60.3%)	
Tertiary lymph node	No	47 (38.2%)	76 (61.8%)	0.658¶
	Yes	32 (41.6%)	45 (58.4%)	

* Fisher's Exact test, ¶ Independent samples t test

Downstaging occurred in 39.5% of patients (Table 2). It was significantly associated with tumor type but showed no significant association with age or treatment type. No significant association was found between downstaging and the presence of TLS, which is consistent with prior reports in which TLS primarily correlated with treatment response rather than with changes in anatomic staging.

Regression scores varied across tumor types, with well-differentiated adenocarcinomas more frequently achieving higher regression grades (Table 3). The presence of TLS showed a mild, non-significant trend toward higher regression grades (2–3), which aligns with previous studies indicating that tumors harboring TLS tend to exhibit better pathological response to CRT.

Table 3. Comparing study variables based on tumor regression status

Variable	Status	Regression score				P value
		3	2	1	0	
Age (Year, Mean ± SD)		61.8 ± 11.7	58.0 ± 12.5	60.7 ± 11.3	61.9 ± 12.7	0.420*
Tumor type	Poorly differentiated adenocarcinoma	0 (0%)	0 (0%)	5 (41.7%)	7 (58.3%)	<0.001¶
	Moderately differentiated adenocarcinoma	0 (0%)	0 (0%)	4 (44.4%)	5 (55.6%)	
	Well differentiated adenocarcinoma	36 (20.8%)	43 (24.9%)	68 (39.3%)	26 (15.0%)	
	SCC	0 (0%)	0 (0%)	2 (100%)	0 (0%)	
	Signet Cell	0 (0%)	0 (0%)	0 (0%)	2 (100%)	
	Mucinous	0 (0%)	0 (0%)	0 (0%)	2 (100%)	
Treatment	Chemotherapyalone	1 (7.1%)	1 (7.1%)	10 (71.4%)	2 (14.3%)	0.046¶
	Radiotherapyalone	4 (57.1%)	1 (14.3%)	2 (28.6%)	0 (0%)	
	Chemoradiotherapy	31 (17.3%)	41 (22.9%)	67 (37.4%)	40 (22.3%)	
Tertiary lymph node	No	26 (21.1%)	23 (18.7%)	43 (35.0%)	31 (25.2%)	0.065¶
	Yes	11 (14.3%)	20 (26.0%)	36 (46.8%)	10 (13.0%)	

* One-way ANOVA, ¶ Independent samples t test

Mean disease-free survival did not differ significantly according to downstaging (P = 0.548) or regression score (P = 0.617) (Table 4). Tumor type had a significant impact on disease-free survival (P < 0.001), with poorly and moderately differentiated adenocarcinomas associated with shorter disease-free intervals. Treatment modality also influenced outcomes (P = 0.001), with radiotherapy alone showing the longest disease-free survival (4.86 years), followed by chemoradiotherapy (4.08 years) and chemotherapy alone (2.79 years). A borderline association was observed between tertiary lymphoid structures (TLS) and disease-free survival (P = 0.062); however, this relationship was not strong enough to establish a

definitive prognostic role. In line with previous studies, tumors exhibiting TLS generally demonstrate more favorable response patterns to chemoradiotherapy, and the present findings are broadly consistent with this trend.

Simple linear regression analysis demonstrated that downstaging was not a significant predictor of disease-free years. The ANOVA results indicated that the model was not statistically significant ($F = 0.828$, $p = 0.364$). The regression coefficient for downstaging was −0.197, suggesting a weak negative association; however, this effect was not statistically significant ($t = -0.910$, $p = 0.364$). The standardized coefficient (Beta = −0.065) was minimal, further indicating that downstaging alone is not a meaningful predictor of disease-free survival.

Similarly, regression score was not a significant predictor of disease-free years. The model yielded $R = 0.031$, $R^2 = 0.001$, and adjusted $R^2 = -0.004$, indicating that regression explained only 0.1% of the variance. The standard error of the estimate was 1.49996, compared with a mean disease-free survival of approximately 4 years. ANOVA results showed $F = 0.197$ and $p = 0.658$, confirming the lack of statistical significance. The regression coefficient was 0.047 ($t = 0.443$, $p = 0.658$), with a very small standardized coefficient (Beta = 0.031), reflecting a negligible and non-significant association.

Logistic regression analysis revealed that tumor regression significantly predicted mortality, whereas downstaging did not. The model constant was −2.143 ($p = 0.000$), with Exp(B) = 0.117. After inclusion of predictors, the −2 log likelihood was 129.929, with Cox & Snell $R^2 = 0.022$ and Nagelkerke $R^2 = 0.045$, indicating that the model explained approximately 2.2% to 4.5% of the variance in mortality. The Hosmer–Lemeshow test showed $\chi^2 = 3.418$ ($p = 0.491$), indicating good model fit. Downstaging was not a significant predictor ($B = -0.290$, $p = 0.600$, Exp(B) = 0.748). In contrast, regression was significantly associated with mortality ($B = 0.568$, $p = 0.046$, Exp(B) = 1.765; 95% CI: 1.011–3.082), corresponding to a 76.5% increase in mortality risk per unit increase in regression score. The final model constant was −2.704 ($p = 0.002$).

Table 4. Comparing disease-free years based on study variables

Variable	Status	Disease-free years (Year, Mean ± SD)	P value
Downstaging	Positive	4.14 ± 1.15	0.548*
	Negative	3.94 ± 1.68	
Regression score	3	3.97 ± 0.77	0.617¶
	2	3.93 ± 1.26	
	1	4.06 ± 1.61	
	0	4.07 ± 1.94	
Tumor type	Poorly differentiated adenocarcinoma	2.42 ± 1.44	<0.001¶
	Moderately differentiated adenocarcinoma	2.89 ± 1.69	
	Well differentiated adenocarcinoma	4.13 ± 1.40	
	SCC	6.00 ± 0.0	
	Signet Cell	6.00 ± 0.0	
	Mucinous	6.00 ± 0.0	
Treatment	Chemotherapyalone	2.79 ± 1.48	0.001¶
	Radiotherapyalone	4.86 ± 0.90	
	Chemoradiotherapy	4.08 ± 1.47	
Tertiary lymph node	No	4.25 ± 1.23	0.062*
	Yes	3.65 ± 1.80	

* Mann-Whitney U test, ¶ Kruskal Wallis test

Discussion

The primary objective of this retrospective cohort study was to evaluate the relationship between pathological response patterns—specifically tumor downstaging and tumor regression—and patient survival outcomes. The analysis revealed a notable and somewhat paradoxical finding: while neither downstaging nor regression significantly predicted disease-free survival (DFS), tumor regression grade emerged as a significant predictor of mortality.

The observed dissociation between DFS and mortality contrasts with the prevailing concept that improved survival is primarily mediated through

reduced recurrence. Typically, a factor associated with mortality is also expected to correlate with DFS; therefore, this discrepancy may reflect the influence of competing risks or distinct biological mechanisms driving early mortality. In the present study, logistic regression analysis demonstrated that tumor regression significantly predicted mortality (B = 0.568, p = 0.046), corresponding to a 76.5% increase in mortality risk per unit increase in regression score, whereas downstaging showed no significant effect on either outcome.

These findings suggest that Dworak regression grades may capture aspects of tumor biology—such as intrinsic aggressiveness—that are not reflected by anatomical downstaging. While downstaging represents a reduction in tumor burden, it does not necessarily indicate favorable tumor biology. In this cohort, tumor type and differentiation were strongly associated with mortality, supporting the hypothesis that poorly differentiated and biologically aggressive tumors may contribute to early mortality through mechanisms independent of conventional recurrence pathways, including rapid systemic progression or perioperative complications.

The lack of association between downstaging and DFS contrasts with established evidence indicating that post-treatment pathological stage (ypTNM) is a strong predictor of long-term outcomes (8–10). Similarly, tumor regression grade (TRG) is widely recognized as an independent prognostic factor for DFS, with higher regression grades and pathological complete response (pCR) consistently associated with improved survival (13–15). Studies by Beddy et al. and Kong et al. have demonstrated strong correlations between favorable regression patterns and improved DFS and overall survival (18, 19).

The absence of statistical significance for DFS in this study may be partly explained by the relatively short follow-up period (2022–2024), which may be insufficient for capturing long-term recurrence events. It is plausible that the mortality signal observed reflects early deaths among patients with highly aggressive tumors, whereas recurrence events in intermediate-risk groups have not yet reached sufficient frequency to demonstrate statistical significance.

A borderline association was observed between tertiary lymphoid structures (TLS) and DFS (p = 0.062), although this did not reach statistical significance. This finding is generally consistent with previous studies suggesting that TLS are associated with improved response to chemoradiotherapy rather than direct effects on anatomical staging. The observation that immune-related features such as TLS and cellular response (regression) may be more biologically informative than anatomical downstaging further supports the importance of tumor microenvironment and host immune response in determining outcomes.

Although both downstaging and regression are widely regarded as key prognostic markers, the present data support only a limited role for downstaging in predicting outcomes within this cohort. The relatively high rates of tumor regression (including 18.0% complete response and 39.5% downstaging) are generally associated with favorable prognosis and may explain the relatively low overall mortality rate of 10.5%. Favorable regression profiles (TRG 2–3) have been linked to improved oncologic outcomes and may assist in postoperative risk stratification, whereas poor regression (TRG 0–1) is associated with worse prognosis and may identify patients who could benefit from intensified adjuvant therapy.

Several limitations should be considered when interpreting these findings. The sample size of 200 patients and relatively low mortality rate limit statistical power, particularly for multivariable analyses, as reflected by borderline significance levels and wide confidence intervals. The short follow-up duration restricts the ability to accurately assess long-term DFS. Additionally, the retrospective design introduces potential selection bias, and the absence of molecular data (e.g., MSI status, KRAS/BRAF mutations) may result in unmeasured confounding. The use of the Dworak grading system, while valid, may also limit comparability with studies using newer regression classification systems.

Conclusion

This study demonstrates that neither downstaging nor tumor regression significantly influences disease-free survival in rectal cancer patients following neoadjuvant therapy. However, tumor regression emerges as a significant predictor of mortality, whereas downstaging does not.

Among the 200 patients, the overall mortality rate was 10.5%. Tumor type and degree of differentiation showed clear associations with mortality, underscoring the importance of intrinsic tumor biology in determining outcomes. Although tertiary lymphoid structures (TLS) demonstrated a statistical association in univariable analysis, this finding should be interpreted cautiously, as prior evidence more consistently links TLS with improved treatment response rather than adverse outcomes, and the present study was not powered to establish an independent prognostic role.

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Authors' Contributors

None.

Data Availability

The data supporting the results of this study are available upon request from the corresponding author.

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Ethics Approval

The study was conducted as a retrospective cohort analysis involving 200 patients treated between 2022 and 2024 at a private pathology laboratory in Isfahan, Iran. Statistical analysis was performed using IBM SPSS version 27.0.

Consent to Participate:

Follow-up data, including recurrence status, were obtained through direct contact with patients or their companions. The study utilized an open-access article distribution under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

Conflict of Interest

The authors declared no conflict of interest.

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