**ARAŞTIRMA MAKALESİ /** *RESEARCH ARTICLE*

# Histopathological Parameters After Neoadjuvant Therapy in Rectal Tumors and Their Relationship with Treatment Response and Prognosis

## *Rektum Tümörlerinde Neoadjuvan Tedavi Sonrası Histopatolojik Parametrelerin Tedavi Yanıtı ve Prognoz ile İlişkisi*

**Ozgecan Hamdemir[1], Semin Ayhan[2], Omer Atmis[2], Omer Acar[3]**

*[1]Department of Pathology, Faculty of Medicine, Kafkas University, Kars; [2]Department of Pathology, Faculty of Medicine, Celal Bayar University, Manisa; [3]Department of Medical Oncology, Kiziltepe State Hospital, Mardin, Türkiye*

## ABSTRACT

***Aim:*** *This study aimed to evaluate histopathological parameters following neoadjuvant therapy in rectal adenocarcinoma and their associations with treatment response and survival outcomes.*

***Materials and methods:*** *A total of 65 patients with rectal adenocarcinoma treated with neoadjuvant chemoradiotherapy followed by surgical resection between 2007 and 2018 were retrospectively analyzed. Histopathological features, including tumor budding, poorly differentiated clusters (PDC), lymphovascular invasion (LVI), perineural invasion (PNI), circumferential resection margin (CRM) status, depth of invasion, and lymph node involvement, were re-evaluated. Tumor regression was graded using the Ryan tumor regression system and dichotomized into good (Grade 0–1) and poor (Grade 2–3) response groups. Survival analyses were performed using the Kaplan–Meier method.*

***Results:*** *Fourteen cases (21.5%) demonstrated a good response, whereas 51 (78.5%) showed a poor response. High tumor budding was significantly associated with reduced treatment response (p <0.001). Perineural invasion and CRM positivity were significantly associated with worse overall survival (p=0.001 and p=0.014, respectively). Lymph node metastasis and greater depth of invasion showed trends toward poorer survival outcomes, although statistical significance was not reached. Patients older than 55 years had significantly longer disease-free survival (p=0.021). Although favorable pathological response was associated with improved survival curves, this difference was not statistically significant.*

***Conclusion:*** *Tumor budding, perineural invasion, and CRM positivity are important prognostic indicators in rectal adenocarcinoma following neoadjuvant therapy. Comprehensive histopathological evaluation of post-treatment specimens plays a critical role in predicting treatment response and long-term outcomes.*

**Key words:** *rectal cancer; neoadjuvant chemoradiotherapy; tumor regression grading; tumor budding; perineural invasion; circumferential resection margin*

## ÖZET

***Amaç:*** *Bu çalışma, rektal adenokarsinomda neoadjuvan tedavi sonrası histopatolojik parametreleri değerlendirmeyi ve bu parametrelerin tedavi yanıtı ile sağkalım sonuçlarıyla ilişkisini incelemeyi amaçladı.*

***Gereç ve Yöntem:*** *2007–2018 yılları arasında neoadjuvan kemoradyoterapi uygulanıp cerrahi rezeksiyon yapılan toplam 65 rektal adenokarsinom hastası retrospektif olarak analiz edildi. Tümör tomurcuklanması, az diferansiye kümeler (PDC), lenfovasküler invazyon (LVI), perinöral invazyon (PNI), sirkumferansiyel rezeksiyon sınırı (CRM) durumu, invazyon derinliği ve lenf nodu tutulumu gibi histopatolojik özellikler yeniden değerlendirildi. Tümör regresyonu Ryan tümör regresyon derecelendirme sistemi kullanılarak değerlendirildi ve iyi (Grade 0–1) ve kötü (Grade 2–3) yanıt gruplarına ayrıldı. Sağkalım analizleri Kaplan–Meier yöntemi ile yapıldı.*

***Bulgular:*** *On dört olgu (%21,5) iyi yanıt, 51 olgu (%78,5) ise kötü yanıt göstermiştir. Yüksek tümör tomurcuklanması, tedavi yanıtında azalma ile anlamlı olarak ilişkili bulunmuştur (p=0,002). Perinöral invazyon ve CRM pozitifliği, daha kötü genel sağkalım ile anlamlı olarak ilişkili saptanmıştır (sırasıyla p=0,001 ve p=0,014). Lenf nodu metastazı ve artmış invazyon derinliği daha kötü sağkalım ile ilişkili eğilim göstermiş, ancak istatistiksel anlamlılık elde edilememiştir. 55 yaş üzeri hastalarda hastalıksız sağkalımın anlamlı olarak daha uzun olduğu görülmüştür (p=0,021). Patolojik olarak iyi yanıt gösteren hastalarda sağkalım eğrileri daha iyi olmakla birlikte bu fark istatistiksel olarak anlamlı bulunmamıştır.*

***Sonuç:*** *Tümör tomurcuklanması, perinöral invazyon ve CRM pozitifliği, neoadjuvan tedavi sonrası rektal adenokarsinomda önemli prognostik belirteçlerdir. Tedavi sonrası örneklerin kapsamlı histopatolojik değerlendirilmesi, tedavi yanıtı ve uzun dönem sonuçların öngörülmesinde kritik rol oynamaktadır.*

**Anahtar kelimeler:** *rektum kanseri; neoadjuvan kemoradyoterapi; tümör regresyon derecelendirmesi; tümör tomurcuklanması; perinöral invazyon; sirkumferansiyel rezeksiyon sınırı*

***İletişim/Contact:*** *Özgecan Hamdemir, Department of Pathology, Faculty of Medicine, Kafkas University, Kars, Türkiye* • ***Tel:*** *0554 682 51 01* • ***E-mail:*** *ozgecandemir_92@hotmail.com* • ***Geliş/Received:*** *09.12.2025* • ***Kabul/Accepted:*** *11.05.2026*

***ORCID:*** *Özgecan Hamdemir, MD: 0000-0001-7204-1627* • *Semin Ayhan, MD: 0000-0002-8546-0705* • *Ömer Atmış, MD: 0000-0003-4789-0875* • *Ömer Acar, MD: 0000-0003-4408-1976*

## Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality (1). Rectal cancer represents a distinct clinical entity within CRC, characterized by specific anatomical, biological, and therapeutic features (2). Prognosis is largely determined by tumor stage and treatment response (3–5).

Neoadjuvant chemoradiotherapy has become the standard of care for patients with locally advanced rectal cancer (stage II–III) (6,7). Preoperative treatment reduces tumor size, improves resectability, and lowers local recurrence rates (7). However, its impact on overall survival remains controversial (8,9), and treatment response varies considerably among patients (8,10).

Pathological complete response (pCR) is an important indicator of therapeutic efficacy and is associated with improved oncological outcomes (11,12). Consequently, tumor regression grading and other histopathological parameters have gained increasing importance in evaluating treatment response (8,10). In addition, emerging strategies such as the "watch-and-wait" approach further highlight the need for accurate pathological assessment (11,12).

Despite numerous studies on neoadjuvant treatment outcomes, uncertainty persists regarding which histopathological features best predict response and long-term prognosis (8,9,13). Identifying reliable pathological parameters may improve risk stratification and guide individualized treatment strategies.

The primary aim of this study was to evaluate the relationship between histopathological parameters and treatment response in rectal cancer following neoadjuvant therapy. The secondary aim was to investigate their association with prognostic factors.

## Material and Methods

### *Ethical Statement*

This retrospective study was conducted in accordance with institutional ethical standards and the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee prior to the initiation of the study.

### *Cases*

A total of 65 patients with rectal carcinoma who received neoadjuvant therapy followed by surgical resection between 2007 and 2018 were retrieved from the archives of the Department of Medical Pathology. All available slides were reviewed, and histopathological findings were re-evaluated.

### *Clinical and Follow-up Data*

The study group's medical oncologist obtained clinical and follow-up data. Complete follow-up data were available for 46 patients; therefore, survival analyses were restricted to this subgroup.

### *Histopathological Evaluation*

All hematoxylin and eosin (H&E)-stained sections were re-examined for histological type, tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), tumor budding, poorly differentiated clusters (PDC), lymphocytic response, mucinous differentiation, depth of invasion, tumor deposits, lymph node status, and tumor perforation.

Tumors were classified according to the WHO Classification of Tumors (2019), staged using the AJCC 8th edition (2017), and evaluated in accordance with CAP (2021) guidelines. Macroscopic findings were obtained retrospectively from pathology reports.

Mucinous adenocarcinomas were excluded from analyses evaluating treatment response and focal mucinous differentiation.

### *Tumor Regression Grading*

Tumor regression was assessed using the Ryan tumor regression grading system recommended by the College of American Pathologists (CAP). The Ryan tumor regression grading system is summarized in Table 1.

To improve statistical power, the four-tiered system was dichotomized into two groups:

- Good response: Grade 0–1
- Poor response: Grade 2–3

### *Statistical Analysis*

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Associations between categorical variables were evaluated using Pearson's chi-square or Fisher's exact

***Table 1.*** *Ryan tumor regression grading system*

| Ryan grade | Definition |
|---|---|
| Grade 0 | Pathologic complete response — no viable tumor cells identified. |
| Grade 1 | Near-complete response — rare residual tumor cells, mostly scattered within fibrosis. |
| Grade 2 | Partial response — easily identifiable viable tumor cells with evidence of treatment effect within fibrotic areas. |
| Grade 3 | Poor response — extensive viable tumor with minimal or no evidence of treatment effect. |

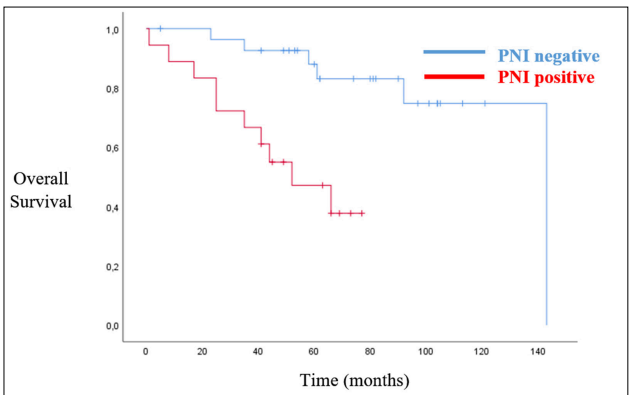


***Figure 1.*** *Kaplan-Meier overall survival curves according to perineural invasion (PNI).*

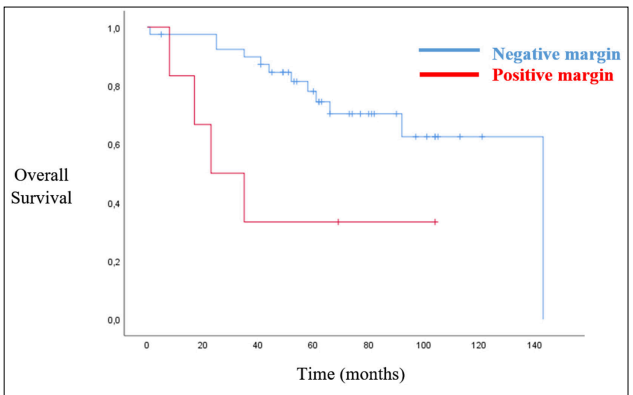


***Figure 2.*** *Kaplan-Meier overall survival curves according to radial surgical margin status.*

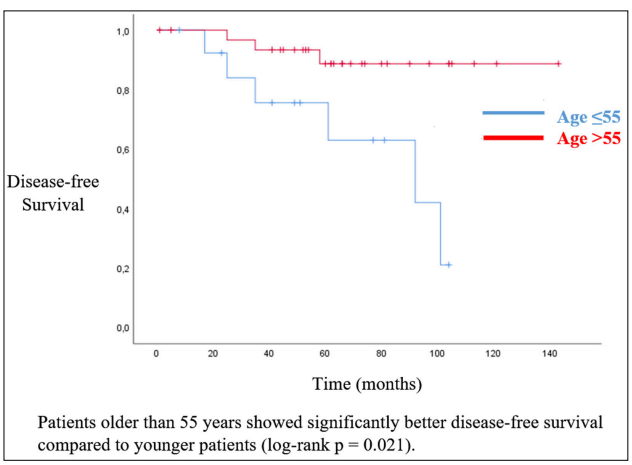


***Figure 3.*** *Kaplan-Meier disease-free survival curves by age groups.*

test. Survival was analyzed using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. A p-value <0.05 was considered statistically significant, while values between 0.05 and 0.10 were considered borderline significant.

## Results

### *Patient Characteristics*

A total of 65 patients were included. Detailed clinicopathological characteristics are presented in Table 2.

According to the Ryan classification, 14 cases (21.5%) demonstrated a good response, whereas 51 (78.5%) showed a poor response following neoadjuvant therapy.

Follow-up data were available for 46 patients. During follow-up, 16 patients (34.8%) died, and 30 (65.2%) were alive. Local recurrence occurred in 8 patients (17.4%).

### *Treatment Response and Clinicopathological Parameters*

High tumor budding was significantly associated with reduced treatment response (p <0.001) (Table 3).

Higher PDC levels, tumor deposits, PNI, and LVI were more frequently observed in the poor response group; however, these associations did not reach statistical significance. No significant associations were observed for other parameters.

### *Survival Analysis*

#### Overall Survival (OS)

Perineural invasion and CRM positivity were significantly associated with reduced overall survival (p=0.001 and p=0.014, respectively) (Fig. 1 and Fig. 2).

***Table 2.*** *Clinicopathological characteristics of the study cohort*

| Categorical variables | Category | n (%) |
|---|---|---|
| Histopathological type | Adenoma-like | 2 (3.1) |
| | Mucinous | 2 (3.1) |
| | NOS | 60 (92.3) |
| | Serrated | 1 (1.5) |
| Degree of differentiation | Well differentiated | 60 (95.2)* |
| | Poorly differentiated | 3 (4.8)* |
| Poorly differentiated clusters | Low | 24 (36.9) |
| | Intermediate | 26 (40.0) |
| | High | 15 (23.1) |
| Tumor budding | Low | 25 (38.5) |
| | Intermediate | 21 (32.3) |
| | High | 19 (29.2) |
| Intratumoral lymphocytic response | Low | 30 (46.2) |
| | High | 35 (53.8) |
| Peritumoral lymphocytic response | Absent | 36 (55.4) |
| | Low | 29 (44.6) |
| Crohn-like reaction | Absent | 42 (64.6) |
| | Present | 23 (35.4) |
| Lymphovascular invasion (LVI) | Absent | 30 (46.2) |
| | Present | 35 (53.8) |
| Venous invasion | Absent | 59 (90.8) |
| | Present | 6 (9.2) |
| Perineural invasion (PNI) | Absent | 42 (64.6) |
| | Present | 23 (35.4) |
| Depth of invasion | T3–T4 | 46 (70.8) |
| | T1–T2 | 19 (29.2) |
| Focal mucinous differentiation | Absent | 53 (84.1)* |
| | Present | 10 (15.9)* |
| Sex | Male | 40 (61.5) |
| | Female | 25 (38.5) |
| Neoadjuvant treatment response | Good response | 14 (21.5) |
| | Poor response | 51 (78.5) |
| Perforation | Absent | 58 (89.2) |
| | Present | 7 (10.8) |
| Lymph node metastasis | Absent | 38 (58.5) |
| | Present | 27 (41.5) |
| Tumor deposit | Absent | 59 (90.8) |
| | Present | 6 (9.2) |
| Distal surgical margin | Negative | 64 (98.5) |
| | Positive | 1 (1.5) |
| Circumferential resection margin (CRM) | Negative | 55 (84.6) |
| | Positive | 10 (15.4) |

| Continuous variables | Mean ± SD | Min–Max |
|---|---|---|
| Age (years) | 62.1 ± 11.3 | 34–84 |
| Tumor size (cm) | 3.75 ± 1.61 | 0.3–8.0 |

* Percentages were calculated excluding mucinous adenocarcinoma cases.
Mucinous adenocarcinoma cases (n = 2) were excluded from analyses involving treatment response and focal mucinous differentiation. Focal mucinous differentiation was evaluated only in non-mucinous tumors.

***Table 3.*** *Association between histopathological parameters and treatment response*

| Parameter | Category | Good response n (%) | Poor response n (%) | p-value |
|---|---|---|---|---|
| Tumor budding | Low | 11 (44.0) | 14 (56.0) | <0.001 |
| | High | 3 (7.5) | 37 (92.5) | |
| Lymphovascular invasion (LVI) | Absent | 9 (30.0) | 21 (70.0) | 0.124 |
| | Present | 5 (14.3) | 30 (85.7) | |
| Perineural invasion (PNI) | Absent | 11 (26.2) | 31 (73.8) | 0.218 |
| | Present | 3 (13.0) | 20 (87.0) | |
| Poorly differentiated clusters (PDC) | Low | 8 (33.3) | 16 (66.7) | 0.206 |
| | High | 6 (14.6) | 35 (85.4) | |
| Tumor deposits | Absent | 14 (23.7) | 45 (76.3) | 0.178 |
| | Present | 0 (0.0) | 6 (100.0) | |

**Disease-Free Survival (DFS)**

Age had a significant effect on disease-free survival (p=0.021), with patients older than 55 years demonstrating longer DFS (Fig. 3).

**Treatment Response and Survival**

Patients with a good pathological response demonstrated better overall survival curves; however, this difference did not reach statistical significance. Similarly, no significant difference in DFS was observed between response groups.

## Discussion

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision is the standard treatment for locally advanced rectal cancer (6,7). However, therapy-induced morphological alterations may complicate pathological assessment (9,10). Although several tumor regression grading systems have been proposed, variability in prognostic correlation and interobserver reproducibility remain challenges (8–10). In addition, CRT may alter established prognostic parameters such as tumor stage, lymph node status, and circumferential resection margin, highlighting the critical role of surgical pathologists in post-treatment evaluation (14–17).

### *Tumor Budding*

Tumor budding is a well-established adverse prognostic factor in colorectal carcinoma and has been associated with advanced stage, lymphovascular invasion, lymph node metastasis, and reduced survival (13,18,19).

In the present study, high tumor budding was significantly associated with poor histopathological response to neoadjuvant therapy. This finding supports the concept that tumor budding reflects aggressive tumor biology and may identify subclones with reduced sensitivity to treatment, in line with previous studies demonstrating its prognostic significance (13,18).

The persistence of tumor budding following neoadjuvant therapy may indicate selective survival of more resistant tumor cell populations. Therefore, assessment of tumor budding in post-treatment specimens may provide additional prognostic information and contribute to more accurate risk stratification.

### *Patient Age*

Colorectal cancer is most commonly diagnosed in older adults (1); however, its incidence among younger patients has increased in recent years (20). Although advanced age is generally considered an adverse prognostic factor, its relationship with survival outcomes remains heterogeneous across different clinical and biological contexts.

In the present study, age was not associated with response to neoadjuvant therapy. However, patients older than 55 years demonstrated significantly longer disease-free survival and a trend toward improved overall survival. This finding contrasts with some reports indicating poorer outcomes in older patients, but several factors may explain this observation.

Patients selected for neoadjuvant therapy at older ages are often physiologically fit, which may contribute to more favorable outcomes. In contrast, tumors arising in younger patients may exhibit more aggressive biological behavior, potentially leading to earlier disease progression despite similar pathological response. Differences in tumor biology, including molecular

characteristics and tumor kinetics, may therefore underlie the observed survival patterns.

Overall, these findings suggest that age alone may not determine treatment response but may influence survival outcomes in a context-dependent manner.

### *Radial Surgical Margin (CRM)*

Circumferential resection margin (CRM) status is a well-established pathological parameter associated with local recurrence and overall survival in rectal cancer (14–16). Although definitions vary, a 1-mm cutoff is widely accepted for CRM positivity (15). Previous studies have demonstrated that CRM involvement — particularly due to direct tumor extension— is associated with an increased risk of recurrence (14,15).

In the present study, CRM status was not associated with response to neoadjuvant therapy, as similar positivity rates were observed in both response groups. This finding suggests that CRM involvement may be more strongly influenced by baseline tumor extent and anatomical factors rather than treatment-induced regression.

Despite the lack of association with treatment response, CRM positivity was significantly associated with worse overall survival, in line with previous studies (14,16). Although the association with disease-free survival did not reach statistical significance, a trend toward better outcomes was observed in CRM-negative patients.

### *Lymph Node Positivity*

Lymph node involvement remains one of the most important prognostic factors in rectal cancer, regardless of neoadjuvant therapy (3–5,21). Although chemoradiotherapy may reduce lymph node yield, accurate nodal evaluation remains essential for staging and prognostic assessment (22–24).

In our cohort, lymph node metastasis was not associated with response to neoadjuvant therapy. Although a slightly higher proportion of good responders was observed among node-positive patients, this difference was not statistically significant.

Survival analyses demonstrated lower overall and disease-free survival in patients with lymph node metastasis, consistent with its established adverse prognostic impact (3–5,21). However, these differences did not reach statistical significance, likely due to the limited sample size.

### *Perineural and Lymphovascular Invasion*

Lymphovascular invasion (LVI) and perineural invasion (PNI) are recognized adverse prognostic factors in colorectal cancer, although their significance after neoadjuvant chemoradiotherapy (CRT) remains variably reported (17,25,26).

In the present study, absence of LVI was associated with a higher proportion of good treatment responses; however, this difference was not statistically significant. Similarly, LVI was associated with lower overall and disease-free survival, but these associations did not reach statistical significance, consistent with previously reported variability in the post-CRT setting (25,27).

Perineural invasion showed a similar pattern in treatment response, with lower rates of good response in PNI-positive cases, though not statistically significant. In contrast, PNI was significantly associated with poorer overall survival, consistent with its established adverse prognostic role (17,26). While disease-free survival did not differ significantly, a trend toward improved DFS was observed in PNI-negative patients.

Overall, these findings suggest that PNI retains prognostic relevance following neoadjuvant therapy, whereas the impact of LVI appears less pronounced in this setting.

### *Pathological Stage*

Pathological stage remains a key prognostic determinant in rectal cancer, including in patients treated with neoadjuvant chemoradiotherapy (3–5,17,28).

In this study, deeper tumor invasion (T3-T4) was associated with a higher proportion of poor treatment responses; however, this association was not statistically significant. Greater depth of invasion was also associated with worse overall survival, consistent with previous reports emphasizing the prognostic value of post-treatment staging (3–5), although statistical significance was not achieved. Disease-free survival did not differ significantly between invasion groups.

These findings suggest that, within this cohort, pathological stage was not independently associated with treatment response or recurrence risk, possibly due to the limited sample size.

### *Response to Neoadjuvant Therapy*

Neoadjuvant chemoradiotherapy induces variable degrees of tumor regression in rectal carcinoma, and

pathological complete response (pCR) has been consistently associated with improved oncologic outcomes (8,10–12). Accurate assessment of tumor regression requires careful macroscopic sampling and histopathological evaluation of the tumor bed (9,10).

In our cohort, patients with a favorable pathological response demonstrated consistently better overall and disease-free survival curves, in agreement with previous studies (11,12). Although these differences did not reach statistical significance, the observed separation of survival curves supports the established association between improved pathological response and favorable long-term outcomes.

The lack of statistical significance is most likely attributable to the limited sample size rather than absence of clinical relevance. These findings further emphasize the importance of pathological response assessment as a complementary prognostic indicator in patients undergoing neoadjuvant therapy.

### *Limitations*

This study has several limitations. First, its retrospective design may introduce selection bias. Second, the sample size was relatively small, particularly in subgroup analyses, which may have limited the study's statistical power. Third, survival analyses were restricted to a subset of patients with available follow-up data. Finally, the lack of molecular data precluded further evaluation of underlying biological differences between subgroups. In addition, the absence of multivariable survival analyses limits the ability to determine the independent prognostic impact of individual parameters.

## Conclusion

In this cohort of rectal adenocarcinoma patients treated with neoadjuvant therapy, key histopathological parameters were evaluated in relation to treatment response and survival outcomes. Tumor budding was significantly associated with poor therapeutic response, highlighting its role as a marker of aggressive tumor biology and potential treatment resistance.

Perineural invasion and circumferential resection margin positivity were significantly associated with worse overall survival, confirming their prognostic relevance in the post-neoadjuvant setting. Although lymph node metastasis and greater depth of invasion showed trends toward poorer outcomes, statistical significance was not reached, likely due to the limited sample size.

Patients older than 55 years demonstrated longer disease-free survival, suggesting potential biological differences between early- and late-onset rectal cancer.

Taken together, these findings support integrating tumor budding, PNI, and CRM status into routine post-neoadjuvant pathological evaluation to improve risk stratification and guide individualized patient management.

Larger prospective studies are needed to validate these findings.

### *Funding*

No financial support was received.

### *Conflict of Interest Statement*

The authors declare no conflict of interest.

## References

1. Siegel RL, Miller KD, Sauer AG, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145–164. https://doi.org/10.3322/caac.21601
2. Benson AB, Venook AP, Adam M, Chang G, Chen YJ, Ciombor KK, et al. NCCN Guidelines Insights: Rectal Cancer, Version 3. 2024. J Natl Compr Canc Netw. 2024;22(6):366–375. https://doi.org/10.6004/jnccn.2024.0041
3. Delitto D, Loftus TJ, Iqbal A. Pathologic stage dictates survival after neoadjuvant radiation for rectal cancer. Oncotarget. 2018;9(84):35474–35475. https://doi.org/10.18632/oncotarget.26262
4. Kuo LJ, Liu MC, Jian JJM, Horng CF, Cheng TI, Chen CM, et al. Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy? Ann Surg Oncol. 2007;14(10):2766–2772. https://doi.org/10.1245/s10434-007-9471-z
5. Mahmoud NN. Colorectal cancer: preoperative evaluation and staging. Surg Oncol Clin N Am. 2022;31(2):127–141. https://doi.org/10.1016/j.soc.2021.12.001
6. Chapman BC, Goodman K, Hosokawa P, Gleisner A, Cowan ML, Birnbaum E, et al. Improved survival in rectal cancer patients treated with long-course versus short-course neoadjuvant radiotherapy. J Surg Oncol. 2019;119(4):518–531. https://doi.org/10.1002/jso.25355

7. Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local cancer recurrence: realities, challenges, and opportunities for new therapies. CA Cancer J Clin. 2018;68:488–505. https://doi.org/10.3322/caac.21498
8. Laohawiriyakamol S, Chaochankit W, Wanichsuwan W, Kanjanapradit K, Laohawiriyakamol T. Tumor regression grade and 5-year overall survival in locally advanced rectal cancer. Ann Coloproctol. 2023;39(1):59–70. https://doi.org/10.3393/ac.2021.01011.0144
9. Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannée G, Bioulac-Sage P, et al. Impact of tumor response on survival after radiochemotherapy in locally advanced rectal carcinoma. Am J Surg Pathol. 2010;34(4):562–568. https://doi.org/10.1097/PAS.0b013e3181d438b0
10. Li JY, Huang XZ, Gao P, Song YX, Chen XW, Lv XE, et al. Survival landscape of tumor regression grades and pathological complete response after neoadjuvant therapy in rectal cancer. BMC Cancer. 2021;21:1214. https://doi.org/10.1186/s12885-021-08922-1
11. Sugumar K, Lie JJ, Stucky CC, Chang YH, Brady J, Wasif N, et al. Pathologic complete response and survival in rectal cancer: a systematic review and meta-analysis. JAMA Netw Open. 2025;8(7):e2521197. https://doi.org/10.1001/jamanetworkopen.2025.21197
12. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with pathological complete response after chemoradiation for rectal cancer. Lancet Oncol. 2010;11(9):835–844. https://doi.org/10.1016/S1470-2045(10)70172-8
13. van Wyk HC, Roseweir A, Alexander P, Park JH, Horgan PG, McMillan DC, et al. Tumor budding, tumor microenvironment, and survival in colorectal cancer. Ann Surg Oncol. 2019;26(13):4397–4404. https://doi.org/10.1245/s10434-019-07931-6
14. Cho MS, Bae HW, Kim NK. Essential knowledge and technical tips for total mesorectal excision in rectal cancer. Ann Coloproctol. 2024;40(4):384–411. https://doi.org/10.3393/ac.2024.00388.0055
15. Detering R, Rutgers MLW, Bemelman WA, Hompes R, Tanis PJ. Prognostic importance of circumferential resection margin in rectal cancer: a systematic review and meta-analysis. Surgery. 2021;170(2):412–431. https://doi.org/10.1016/j.surg.2021.02.029
16. Hugen N, Voorham QJM, Snaebjornsson P, Nagtegaal ID, Beets GL, Loughrey MB. Mode of circumferential margin involvement and its impact on outcomes in rectal cancer. Eur J Surg Oncol. 2024;50:108598. https://doi.org/10.1016/j.ejso.2024.108598
17. Yu L, Yuan J, Lou S, Huang A, Cai X, Ji J, et al. Factors affecting survival in colorectal cancer: an umbrella review. J Transl Med. 2025;23:1185. https://doi.org/10.1186/s12967-025-06876-7
18. Rafiee A, Nasri P, Moradi A, Karimian P. Tumor budding as a prognostic indicator after neoadjuvant chemoradiotherapy in rectal cancer: a systematic review and meta-analysis. Front Oncol. 2025;15:1429319. https://doi.org/10.3389/fonc.2025.1429319
19. Ueno H, Murphy J, Jass JR, Mochizuki H, Talbot IC. Tumour budding as an index of aggressiveness in rectal cancer. Histopathology. 2002;40(2):127–132. https://doi.org/10.1046/j.1365-2559.2002.01324.x
20. Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, et al. Increasing incidence of colorectal cancer in young adults in Europe. Gut. 2019;68(10):1820–1826. https://doi.org/10.1136/gutjnl-2018-317592
21. Yeo SG, Kim DY, Kim TH, Chang HJ, Oh JH, Park W, et al. Prognostic significance of nodal status after chemoradiotherapy in rectal cancer. Ann Surg. 2010;252(6):998–1004. https://doi.org/10.1097/SLA.0b013e3181f3f1b1
22. Abbaspour E, Karimzadhagh S, Monsef A, Joukar F, Mansour-Ghanaei F, Hassanipour S. Radiomics for prediction of lymph node metastasis in colorectal cancer: a systematic review and meta-analysis. Int J Surg. 2024;110:3795–3813. https://doi.org/10.1097/JS9.0000000000001239
23. Dekker JWT, Peeters KC, Putter H, Vahrmeijer AL, van de Velde CJH. Metastatic lymph node ratio in stage III rectal cancer. Eur J Surg Oncol. 2010;36(12):1180–1186. https://doi.org/10.1016/j.ejso.2010.09.007
24. Tan L, Liu ZL, Ma Z, He Z, Tang LH, Liu YL, et al. Prognostic impact of lymph node yield after neoadjuvant therapy in rectal cancer: a meta-analysis. World J Gastrointest Oncol. 2020;12(12):1443–1455. https://doi.org/10.4251/wjgo.v12.i12.1443
25. Kim CH, Yeom S-S, Lee SY, Kim HR, Kim YJ, Lee KH, et al. Prognostic impact of lymphovascular invasion after neoadjuvant chemoradiotherapy. World J Surg 2019;43:260–272. https://doi.org/10.1007/s00268-018-4774-8
26. Koukourakis IM, Kouloulias V, Tiniakos D, Georgakopoulos I, Zygogianni A. Current status of locally advanced rectal cancer therapy and future prospects. Crit Rev Oncol Hematol. 2023;186:103992. https://doi.org/10.1016/j.critrevonc.2023.103992
27. Das P, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Hoff PM, et al. Clinical and pathologic predictors of recurrence and survival in rectal cancer after chemoradiotherapy. Am J Clin Oncol. 2006;29(3):219–224. https://doi.org/10.1097/01.coc.0000214930.78200.4a
28. Weiser MR. AJCC 8th edition: colorectal cancer. Ann Surg Oncol. 2018;25(6):1454–1455. https://doi.org/10.1245/s10434-018-6462-1