GMR
The Original

RESIDUAL NODAL DISEASE AFTER TOTAL NEOADJUVANT THERAPY AND SURGICAL RESECTION FOR RECTAL CANCER: PROGNOSTIC IMPLICATIONS BEYOND PRIMARY TUMOR RESPONSE

Dr Gultaj Ahmad [1], Dr Waseem Akram [2]*, Dr. Fabiha Qayyum [3], Hina Sabeen [4], Dr Arooj Ali [5], Shoaib Hasan [6]

[1] Ayub Teaching Hospital Abbottabad.
[2]*Assistant Professor, People's University of Medical &Health sciences for Women SBA, Pathology Department, Nawabshah SBA
[3] Resident (R2) Diagnostic Radiology Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Punjab, Pakistan
[4] MBBS, LECTURER, PATHOLOGY DEPARTMENT, PUMHS NAWABSHAH
[5] assistant professor pathology department M.Phil. microbiology, CRCP , CHPE
[6] Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore, Pakistan
***Corresponding Author:** Dr Waseem Akram, dr_zardari23@yahoo.com

gultajahmad16@gmail.com [1], dr_zardari23@yahoo.com [2]*, fabihaqayyum@hotmail.com [3], hinasabeen7@gmail.com[4], dr.aroojatif@gmail.com [5], shoaibhasan9293600@gmail.com [6]

ABSTRACT

Background: Total neoadjuvant therapy (TNT) improves major and complete primary tumour response in locally advanced rectal cancer but regression of the rectal wall does not necessarily equate with eradication of regional nodal disease. Goal: To review and synthesize the literature on RPND after neoadjuvant therapy and surgical resection in a critical manner with an emphasis on the prognostic information not provided by the response of the primary tumor.

Methods: A focused narrative review was conducted in the databases of PubMed/MEDLINE, Scopus, Web of Science and Google Scholar. Searches were updated on 19 September 2026 and included terms for rectal cancer, total neoadjuvant therapy, neoadjuvant chemoradiotherapy, ypT0, ypN, lymph-node metastasis, nodal regression, magnetic resonance imaging, watch-and-wait, tumour deposits and circulating tumour DNA. Randomized trials of TNT, systematic reviews, guidelines, and cohort studies reporting post-treatment nodal status or oncologic outcomes were prioritized. Historical chemoradiotherapy cohorts were included when they were relevant to the study of ypT0N positive disease, but were separately analyzed from modern TNT era data.

Results: A meta analysis estimated residual nodal metastasis in around 4.6% of patients who achieved complete response (CR) to neoadjuvant chemoradiotherapy (nCRT) [6]. There were 44 patients with ypT0N1–2 disease in the 2025 cohort of 457 ypT0 patients; the 5-year disease-free survival rate was 84.8% for ypT0N0 and 68.4% for ypT0N1–2, with residual nodal disease independently predicting disease-free survival (adjusted hazard ratio 2.285, 95% CI 1.246–4.192); the overall survival was not significantly different (93.9% vs 88.8%) [12]. A 2025 pathologic study revealed that 29 of 503 patients had ypT0N-positive disease (5.8%), and that histologic regression of the lymph node (LR) was an independent predictor of occult nodal metastasis (odds ratio 4.11, 95% confidence interval 1.71–9.52) [23]. Restaging MRI is still not entirely accurate to rule out microscopic residual nodal disease [15].

Conclusions: In addition to primary-tumour regression, residual nodal disease seems to offer a poor prognosticator of recurrence and disease-free survival. But optimal management in the 21st century after TNT and the effect size after TNT are still unknown as a lot of evidence is retrospective or from before the era of TNT. The postoperative risk assessment should therefore take into account ypN status together with ypT category, margins, tumor deposits, lymphovascular invasion, perineural invasion and other features of residual disease; and molecular residual-disease strategies are investigational.

KEYWORDS: Rectal Cancer, Total neoadjuvant therapy, Residual nodal disease, ypT0N-positive, Lymph node metastasis, Pathologic response, Total mesorectal excision, Disease-free survival

1. INTRODUCTION

Total neoadjuvant therapy (TNT) is an emerging treatment option for locally advanced rectal cancer, since systemic chemotherapy is administered before surgery along with pelvic radiotherapy or chemoradiotherapy. Randomized trials such as RAPIDO, PRODIGE 23, OPRA, and CAO/ARO/AIO-12 proved the clinical importance of TNT and current recommendations favor its use especially for lower rectal tumors and those with a higher risk of local or distant failure [1–5,25].

With the rising number of Achieve complete or near complete response, the focus has shifted from resectability alone to response adapted care and organ preservation. However, a significant interpretive dilemma has been noted—the primary rectal tumour and regional lymph-node metastases do not necessarily regress together. The

patient can have no carcinoma in the bowel wall, but has metastatic carcinoma in the mesorectal nodes. Therefore, the ypT0N-positive phenotype is considered an endogenous model for investigating the information that is not contained in the information from the primary-tumor response [6–13].

This review is on that dissonance. The novelty is not only that ypN positivity is bad, but that the modern TNT era in which systemic therapy is given earlier, organ preservation is being increasingly thought of, and post surgery residual disease could be a more highly selected treatment resistant phenotype in the ypT0N+ literature.

2. Review Approach

This narrative review is designed to be replicable, but not a systematic review. The databases used were PubMed/MEDLINE, Scopus, Web of Science and Google Scholar, and were searched up to 19 September 2026. Examples of core search concepts were combinations of “rectal cancer” and “total neoadjuvant therapy;” “neoadjuvant chemoradiotherapy,” “ypT0,” “ypN,” “residual nodal disease,” “lymph node metastasis,” “nodal regression,” “restaging magnetic resonance imaging (MRI),” “watch-and-wait,” “tumor deposits,” “lymphovascular invasion,” and “perineural invasion,” and “circulating tumor DNA.”

Randomized trials were included if they defined TNT, guideline documents, systematic reviews and meta-analyses, and observational studies reporting on the frequency of ypT0N status, recurrence, disease-free survival, overall survival, or accuracy of nodal restaging were included. Studies were excluded if it was difficult to determine the outcomes for the nodes from overall pathologic response; if it was difficult to distinguish rectal cancer from colon cancer; or if the report did not give an interpretable cancer result. Key articles' reference lists were hand searched for additional relevant studies.

Due to the limited use of TNT in the West, the evidence was divided conceptually into historical/conventional neoadjuvant chemoradiotherapy (CRT) cohorts, mixed-era cohorts which contained both TNT and conventional therapy, and modern TNT therapy trials/guidance. This distinction was retained when interpreting and no older estimates were interpreted as contemporary TNT practice.

3. Residual Nodal Disease Beyond Primary Response

Complete response in the wall of the rectum does not imply complete sterilization of the mesorectum. Several factors, including differences in vascularity, stromal composition, immune context, hypoxia, drug exposure and radiation effect, could play a role in the variable regression of the primary vs. the nodal compartment. In the meta-analysis by Haak et al, the prevalence of ypT0N positive disease after neoadjuvant chemoradiotherapy was 4.61% [6].

Previous series have reported a broad spectrum of residual nodal involvement with some due to differences in baseline staging, therapy, and pathological findings, and others due to differing sample size [7,9–11]. It is therefore not that ypT0N-positive disease is found in a high proportion of patients, but that it occurs with great regularity and clinical significance, calling into question the assertion that complete mural regression equates with complete locoregional response.

4. Prognostic Evidence: Historical and TNT-Era Cohorts

A 333 patients cohort with ypT0 disease following chemoradiotherapy were included in the KROG 09-01 study. 5-year disease-free survival was 88.5% compared to 45.2% for ypT0N+ disease and 5-year overall survival was 94.8% compared to 72.8% for ypT0N+ disease; ypN was the most relevant independent prognostic factor for both endpoints [9].

This is a group before the days of modern-day TNT, but it lay the foundations for the idea that a good first response can be outweighed by maintaining the node for as long as possible. Analysis of 5,683 ypT0 cases on the National Cancer Database (NCDB) showed 527 cases of residual nodal disease. There was no significant difference in the 5-year overall survival between ypT0N-positive and ypT0N-negative disease, which was 80% for the former and 86% for the latter, and nodal positivity was an independent predictor of death (hazard ratio 1.74; 95% confidence interval, 1.33 to 2.28) [7].

More directly applicable to current practice, Elshami et al. compared the results of TNT with 30,751 patients who received neoadjuvant chemoradiotherapy and surgery. The number of ypT0N+ patients were 342, of which 181 patients (52.9%) had received TNT. In the TNT group, there was no clear difference in 5-year OS between ypT0N0 and ypT1-2N0 disease, but ypT0N-positive disease had a lower OS compared to ypT3-4N0 disease and ypT1-2N-positive disease [8]. This indicates that the prognosis is not as good when there is residual nodal disease, which is suggested by complete primary regression. The key studies used in the comparisons are summarized in Table 1.

5. Contemporary 2025 Evidence and a More Calibrated Interpretation

The study by Luo et al. (2025) gives a timely estimate. There were 457 patients with ypT0 disease; 44 of them were treated for ypT0N1-2 disease. Five-year disease-free survival was 84.8% in ypT0N0 and 68.4% in ypT0N1–2 patients (P=0.016). Residual nodal status was an independent predictor of disease-free survival (adjusted hazard ratio 2.285, 95% confidence interval 1.246–4.192; P=0.008) [12].

Importantly, there was no significant difference in overall survival (OS) (93.9% vs. 88.8%, P=0.602) [12]. This separation allows to avoid overstatement. At present, there is evidence for residual nodal disease being a bad prognostic factor, particularly for recurrence and disease-free survival, but no evidence to suggest a statistically significant overall survival disadvantage for all contemporary cohorts.

Table 1. Pivotal evidence on residual nodal disease after major or complete primary tumor response.

Study	Design / n	Treatment era/regimen	ypT0N+	Follow-up	Key outcome	Adjusted effect	Major limitation
Yeo et al. [9]	Multicenter; 333 ypT0	Historical CRT	29/333 (8.7%)	Median 43 mo	5-y DFS 88.5% vs 45.2%; OS 94.8% vs 72.8%	ypN independently predicted DFS/OS	Pre-TNT era
Lorenzon et al. [11]	13-center cohort; 261 ypT0/ypTis	Historical/mixed NAT	8.7% N+	Mean 47.6 mo	91.6% of relapses distant; N+ worse OS	Nodal positivity independently associated with OS	Retrospective; heterogeneous therapy
Lu et al. [10]	Single center; 59 ypT0	CRT	8/59 (13.6%)	Median 52 mo	5-y RFS 82.7% vs 62.5%; OS 90.9% vs 70.0%	ypN+ independently predicted recurrence	Small N+ subgroup
Erkan et al. [7]	NCDB; 5,683 ypT0	Neoadjuvant (chemo)RT	527/5,683 (9.3%)	Database survival	5-y OS 86% vs 80%	HR 1.74 (1.33–2.28)	No recurrence endpoint
Haak et al. [6]	Meta-analysis; 7,568	Predominantly CRT	Pooled 4.61%	Varied	Quantified residual nodal risk after ypT0	Meta-regression	Heterogeneous historical cohorts
Elshami et al. [8]	NCDB; 30,751	TNT or CRT + surgery	342; 181 TNT	5-y OS	TNT ypT0N+ worse than ypT0N0/ypT1–2N0	Category-based survival models	Limited regimen/recurrence detail
Luo et al. [12]	Retrospective; 457 ypT0	2012–2022 NAT	44/457 (9.6%)	5-y outcomes	DFS 84.8% vs 68.4%; OS NS	DFS HR 2.285 (1.246–4.192)	Single center; retrospective
Xiao et al. [23]	Retrospective; 503 ypT0	2009–2024 NAT	29/503 (5.8%)	Pathologic endpoint	Regressed nodes enriched in ypT0N+	OR 4.11 (1.71–9.52)	Colorectal cohort; not survival-focused
Loftås et al. [15]	Matched MRI study; 38	Neoadjuvant therapy	19 ypT0N+	Restaging	MRI sensitivity 37%, specificity 84%	Diagnostic study	Small sample

5. Histopathologic Nodal Regression and Occult Metastasis

A newer pathogenic dimension is that of regressed lymph nodes, which demonstrate fibrosis and/or necrosis, acellular mucin, or a foamy-cell reaction in the absence of viable carcinoma. The 2025 retrospective cohort consisted of 503 ypT0 colorectal cancers, with 29 cases (5.8%) having ypT0N disease. Occult nodal metastasis occurred in 38% of ypT0N-positive cases and in 10% of ypT0N0 cases, and was the only independent predictor of occult nodal metastasis (odds ratio 4.11, 95% confidence interval 1.71–9.52) [23].

This discovery takes this binary positive/negative classification of nodal response one step further. Even if no carcinoma remains, there is evidence in the histology that a node had contained the tumor which was treatable at the time. Before regressed-node morphology is used as an integral part of routine risk algorithms, it must be validated prospectively.

6. Imaging: Why ycN0 and ypN0 Are Not Interchangeable

Restaging MRI is also vital for response assessment, and nodal restaging is still challenging. Post therapy nodes may be smaller, less prominent, irregular or fibrotic, even when they meet traditional size criteria. For small nodes in the mesorectum, there is still some uncertainty despite the use of diffusion weighted imaging (DWI) for better assessing the primary tumour [15,26,27].

For patients who had complete luminal response, restaging MRI was able to detect residual nodal disease in only 7 of 19 ypT0N+ patients (37% sensitivity, 84% specificity) [15]. Therefore, radiologic ycN0 should not be

interpreted as equal to pathologic ypN0. An integrated restaging exam should rely on a combination of factors, including morphology, fibrosis, diffusion, mesorectal fascia, extramural vascular invasion, and nodal assessment—these are all factors—rather than just the size of the nodes [26].

7. TNT Trials and the Changing Meaning of Residual Disease

The intensity of treatment and the timing of systemic therapy were changed in RAPIDO, PRODIGE 23, OPRA and CAO/ARO/AIO-12 [1-5]. The long-term benefits of PRODIGE 23 data show a durable disease-control after intensified neoadjuvant systemic therapy [2] and the OPRA study shows organ preservation can be maintained for a long length of time in selected patients with clinical complete response [3]. The changes in these developments modify the definition of ypN-positive disease. Persistent nodal metastases has remained after completed TNT therapy prior to surgery.

This, therefore, suggests some biological significance that the post TNT ypN positive population may represent a particularly selected portion of the population. This hypothesis, however, is more compelling than the direct evidence that is currently available, and prospective cohorts with a more specific TNT exposure should be collected before the strength of this effect is quantifiable. In Figure 1, it is proposed that the primary and nodal responses be evaluated as separate but related aspects prior to integrated postoperative risk assessment.

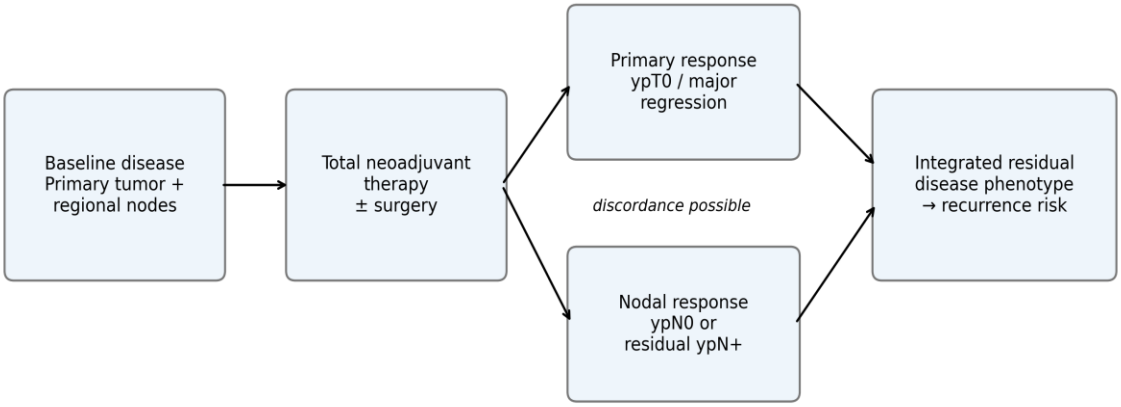

Figure 1. Conceptual framework for discordant primary tumor and nodal response after total neoadjuvant therapy. Primary tumor regression and nodal sterilization are assessed separately and then integrated with other residual-disease features for postoperative risk interpretation.

8. Composite Postoperative Risk Assessment

Post-treatment nodal status should not be interpreted as the only information. Factors influencing prognosis after resection include ypT category, ypN category and nodal burden, circumferential and distal margins, presence of tumour deposits, presence of lymphovascular invasion, presence of perineural invasion, presence of extramural vascular invasion, tumour differentiation, regression grade, and quality of mesorectal resection [19,20,28–30].

Pathologic patterns of both primary and nodal tumors are summarized in Table 2. Therefore, the term ypT0N0 must be separated from the term ypT0N positive disease but must not be used separately from the broader pathologic context. The goal of the practical is not a single-marker hierarchy, but an integrated residual-disease phenotype.

Table 2. Interpretation of combined post-treatment primary tumor and nodal pathologic patterns.

Pattern	Primary response	Nodal response	Interpretation
ypT0N0	Complete	No viable nodal metastasis	True pathologic complete response
ypT1–2N0	Major	No viable nodal metastasis	Substantial downstaging with nodal clearance
ypT3–4N0	Limited/moderate	No viable nodal metastasis	Persistent primary burden despite nodal clearance
ypT0–2N-positive	Complete/major	Residual nodal metastasis	Discordant response; recurrence risk not captured by primary response alone
ypT3–4N-positive	Limited	Residual nodal metastasis	High residual locoregional disease burden

Abbreviations: chemoradiotherapy (CRT); disease-free survival (DFS); hazard ratio (HR); magnetic resonance imaging (MRI); neoadjuvant therapy (NAT); National Cancer Database (NCDB); not statistically significant (NS); odds ratio (OR); overall survival (OS); recurrence-free survival (RFS); total neoadjuvant therapy (TNT).

10. Organ Preservation and the Clinical–Pathologic Information Gap

Watch-and-wait is a clinical complete response—not a pathologic complete response. Nonoperative management of fractures is supported by pooled analyses and subsequent analyses by OPRA, as long as patient selection is careful and monitored carefully [3,18].

The downside is, that mesorectal nodal sterilization is not directly studied, but can only be assumed from imaging and clinical response. This information gap should be made clear. It does not negate organ preservation, but underscores the importance of recognizing CCr as opposed to PCR and the importance of maintaining high-quality MRI, endoscopy, digital rectal exam, multidisciplinary review, and structured surveillance.

11. Circulating Tumor DNA: Promising but Investigational

Circulating tumor DNA is an attractive candidate for complementing anatomic response assessment because it may detect molecular residual disease not visible on imaging. Reviews of locally advanced rectal cancer suggest that post-treatment circulating tumor DNA positivity is associated with residual disease and recurrence risk, but sensitivity remains insufficient for use as a standalone selection tool for nonoperative management [31,32].

Therefore, circulating tumor DNA should currently be presented as a research strategy rather than an established indication for intensified surveillance or additional therapy. A particularly important future question is whether circulating tumor DNA adds prognostic information beyond ypN status in patients who have already completed TNT and undergone resection.

12. Clinical Implications

For patients undergoing total mesorectal excision, pathology reports should clearly distinguish primary-tumor regression from nodal response and should reserve pathologic complete response for ypT0N0 disease. The number of nodes examined, number involved, tumor deposits, margins, and lymphovascular and perineural invasion should be documented.

Residual ypN-positive disease should inform prognostic discussions, but current evidence does not establish a universal post-TNT intervention. Automatically adding postoperative chemotherapy after a completed TNT regimen is not supported for every patient. Management should remain individualized and guideline-concordant [25].

13. Research Priorities

Future studies should enroll contemporary TNT-treated populations, report ypN burden separately from primary regression, and avoid pooling historical chemoradiotherapy with TNT without stratification. Prospective work should test whether regressed-node morphology, circulating tumor DNA, quantitative magnetic resonance imaging, and molecular profiling of residual nodes improve prediction beyond standard pathology.

Trials should also determine whether a residual nodal phenotype identifies patients who benefit from altered surveillance or additional systemic strategies. Until such evidence exists, these approaches should be described as investigational rather than recommended practice.

14. Strengths and Limitations of the Evidence

The strongest feature of the literature is directional consistency: across historical institutional cohorts, national databases, mixed-era studies, and recent series, ypN positivity after major or complete primary response is associated with less favorable outcomes [7–13].

The major limitation is evidence maturity. Much of the literature is retrospective, treatment regimens vary, and several influential studies predate routine TNT. Some databases lack disease-specific recurrence, detailed chemotherapy regimens, magnetic resonance imaging characteristics, and molecular information. Contemporary data also show that the adverse signal may be clearer for disease-free survival than overall survival [12]. These limitations argue for calibrated conclusions rather than deterministic statements.

15. DISCUSSION

This review advances a TNT-era interpretation of residual nodal disease. Earlier studies established that ypT0N-positive disease is prognostically distinct from ypT0N0 disease, but contemporary practice has changed the biological and clinical context in which that observation is used. Systemic therapy is now commonly completed before surgery; clinical complete response may lead to organ preservation; and the residual tissue found at resection has survived a more intensive preoperative treatment course.

Three implications follow. First, primary-tumor response and nodal response should be treated as complementary rather than interchangeable dimensions. Second, the adverse effect of residual nodes should be expressed with endpoint-specific precision: recurrence and disease-free survival signals are consistent, while overall-survival differences are not universal. Third, modern risk stratification should combine nodal status with other residual pathologic and molecular features rather than seeking a single surrogate for treatment success.

The emerging histopathologic concept of regressed lymph nodes adds a further layer. A node without viable tumor may still contain evidence of previous metastatic involvement, while a small apparently benign node on imaging may harbor viable disease. These observations reinforce the need to conceptualize response spatially across the rectal wall, mesorectum, and systemic compartment.

16. CONCLUSION

Residual nodal disease after neoadjuvant treatment and surgical resection provides clinically meaningful prognostic information beyond primary-tumor regression. The most consistent evidence concerns recurrence and disease-free survival, including contemporary data showing inferior 5-year disease-free survival in ypT0N1–2 compared with ypT0N0 disease. Overall-survival effects are less uniform across cohorts.

In the TNT era, ypN status should therefore be integrated with ypT category, nodal burden, margins, tumor deposits, lymphovascular and perineural invasion, and other residual-disease features. The optimal management of ypN-positive disease after completed TNT remains uncertain. Prospective TNT-specific studies are required before intensified surveillance, circulating tumor DNA–guided management, or additional systemic treatment can be recommended on the basis of residual nodal disease alone.

REFERENCES

1. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision versus preoperative chemoradiotherapy, total mesorectal excision, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):29–42. doi:10.1016/S1470-2045(20)30555-6.

2. Conroy T, Castan F, Etienne PL, et al. Total neoadjuvant therapy with modified folinic acid, fluorouracil, oxaliplatin, and irinotecan (mFOLFIRINOX) versus preoperative chemoradiotherapy in patients with locally advanced rectal cancer: long-term results of the UNICANCER-PRODIGE 23 trial. Ann Oncol. 2024;35(10):873–881. doi:10.1016/j.annonc.2024.06.019.

3. Verheij FS, Omer DM, Williams H, et al. Long-term results of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: the randomized phase II OPRA trial. J Clin Oncol. 2024;42(5):500–506. doi:10.1200/JCO.23.01208.

4. Fokas E, Allgäuer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol. 2019;37(34):3212–3222. doi:10.1200/JCO.19.00308.

5. Fokas E, Schlenska-Lange A, Polat B, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: long-term results of the CAO/ARO/AIO-12 randomized clinical trial. JAMA Oncol. 2022;8(1):e215445. doi:10.1001/jamaoncol.2021.5445.

6. Wee IJY, Cao HM, Ngu JCY. The risk of nodal disease in patients with pathological complete responses after neoadjuvant chemoradiation for rectal cancer: a systematic review, meta-analysis, and meta-regression. Int J Colorectal Dis. 2019;34(8):1349–1357. doi:10.1007/s00384-019-03327-w.

7. Erkan A, Mendez A, Trepanier M, Kelly J, Nassif G, Albert MR, Lee L, Monson JRT. Impact of residual nodal involvement after complete tumor response in patients undergoing neoadjuvant (chemo)radiotherapy for rectal cancer. Surgery. 2019;166(4):648–654. doi:10.1016/j.surg.2019.03.026.

8. Elshami M, Goldstone RN, Blaszkowsky LS, Cusack JC Jr, Hong TS, Wo JY, Qadan M. Patient survival with ypT0N+ following neoadjuvant therapy in rectal cancer. Dis Colon Rectum. 2022;65(10):1224–1231. doi:10.1097/DCR.0000000000002186.

9. Yeo SG, Kim DY, Kim TH, et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg. 2010;252(6):998–1004. doi:10.1097/SLA.0b013e3181f3f1b1.

10. Lu Z, Cheng P, Yang F, Zheng Z, Wang X. Long-term outcomes in patients with ypT0 rectal cancer after neoadjuvant chemoradiotherapy and curative resection. Chin J Cancer Res. 2018;30(2):272–281. doi:10.21147/j.issn.1000-9604.2018.02.10.

11. Lorenzon L, Parini D, Rega D, et al. Long-term outcomes in ypT0 rectal cancers: an international multi-centric investigation on behalf of Italian Society of Surgical Oncology Young Board (YSICO). Eur J Surg Oncol. 2017;43(8):1472–1480. doi:10.1016/j.ejso.2017.04.017.

12. Luo D, Wang Z, Yang Y, Li Q, Li X. Prognostic value of residual lymph node status in patients with pathological T0 rectal cancer after neoadjuvant therapy. Ther Adv Gastroenterol. 2025;18:17562848251340494. doi:10.1177/17562848251340494.

13. Zhou J, Sun Y, Xiao L, Lu H, Yin X, Kong Y, Zhang Y, Guo W, Zhou Y. Prognosis and influencing factors of patients with different lymph node statuses after pathological complete response to neoadjuvant chemoradiotherapy in rectal cancer. Oncol Lett. 2025;30(1):359. doi:10.3892/ol.2025.15105.

14. Diefenhardt M, Schlenska-Lange A, Kuhnt T, et al. Total neoadjuvant therapy for rectal cancer in the CAO/ARO/AIO-12 randomized phase 2 trial: early surrogate endpoints revisited. Cancers (Basel). 2022;14(15):3658. doi:10.3390/cancers14153658.

15. Loftås P, Sturludóttir M, Hallböök O, Almlöv K, Arbman G, Blomqvist L. Assessment of remaining tumour involved lymph nodes with MRI in patients with complete luminal response after neoadjuvant treatment of rectal cancer. Br J Radiol. 2018;91(1087):20170938. doi:10.1259/bjr.20170938.

16. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared with long-course chemoradiotherapy and surgery: a 5-year follow-up of the RAPIDO trial. Ann Surg. 2023;278(4):e766–e772. doi:10.1097/SLA.0000000000005799.
17. Fokas E, Williams H, Diefenhardt M, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: pooled analysis of the CAO/ARO/AIO-12 and OPRA randomized phase 2 trials. Eur J Cancer. 2024;210:114291. doi:10.1016/j.ejca.2024.114291.
18. Williams H, Fokas E, Diefenhardt M, et al. Survival among patients treated with total mesorectal excision or selective watch-and-wait after total neoadjuvant therapy: a pooled analysis of the CAO/ARO/AIO-12 and OPRA randomized phase II trials. Ann Oncol. 2025;36(5):543–547. doi:10.1016/j.annonc.2025.01.006.
19. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–1933. doi:10.1200/JCO.2011.40.1836.
20. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol. 2014;32(15):1554–1562. doi:10.1200/JCO.2013.54.3769.
21. Lorenzon L, De Luca R, Santoro G, et al. Pathologic stage of ypT0N+ rectal cancers following neo-adjuvant treatment: clinical interpretation of an orphan status. Pathol Res Pract. 2022;237:154002. doi:10.1016/j.prp.2022.154002.
22. Jang TY, Yu CS, Yoon YS, Lim SB, Hong SM, Kim TW, Kim JH, Kim JC. Oncologic outcome after preoperative chemoradiotherapy in patients with pathologic T0 (ypT0) rectal cancer. Dis Colon Rectum. 2012;55(10):1024–1031. doi:10.1097/DCR.0b013e3182644334.
23. Xiao C, Shen Y, He D, Chen HN. Histopathologic regression in lymph nodes predicts occult metastasis in ypT0 colorectal cancers after neoadjuvant therapy: a retrospective cohort study. Updates Surg. 2025;77(8):2277–2283. doi:10.1007/s13304-025-02407-7.
24. Diefenhardt M, Kosmala R, Fleischmann M, et al. Chemotherapy before or after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer: 5-year results of the CAO/ARO/AIO-12 trial—a general pairwise comparison. ESMO Open. 2025;10(3):104483. doi:10.1016/j.esmoop.2025.104483.
25. Scott AJ, Kennedy EB, Berlin J, et al. Management of locally advanced rectal cancer: ASCO guideline. J Clin Oncol. 2024;42(28):3355–3375. doi:10.1200/JCO.24.01160.
26. ESGAR Rectal Imaging Guideline Group. MRI to guide clinical management of rectal cancer: updated consensus recommendations from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR): Part II—Restaging and response evaluation. Eur Radiol. 2026;36(6):4608–4621. doi:10.1007/s00330-025-12275-9.
27. Horvat N, Miranda J, Nomura CH, et al. Restaging magnetic resonance imaging of the rectum after neoadjuvant therapy: a practical guide. Radiol Bras. 2024;57:e20240004. doi:10.1590/0100-3984.2024.0004.
28. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. 2008;26(2):303–312. doi:10.1200/JCO.2007.12.7027.
29. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. Am J Clin Pathol. 2007;127(2):287–294. doi:10.1309/903UT10VQ3LC7B8L.
30. Betge J, Pollheimer MJ, Lindtner RA, et al. Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. Cancer. 2012;118(3):628–638. doi:10.1002/cncr.26310.
31. Schou JV, Larsen FO, Sørensen BS, et al. Circulating cell-free DNA as predictor of treatment failure after neoadjuvant chemoradiotherapy before surgery in patients with locally advanced rectal cancer. Ann Oncol. 2018;29(3):610–615. doi:10.1093/annonc/mdx778.
32. Yahya J, Baber M, Nabavizadeh N, Goodyear SM, Kardosh A. A review of circulating tumor DNA as a biomarker guide for total neoadjuvant therapy in patients with locally advanced rectal cancer. J Gastrointest Cancer. 2023;54(4):1140–1150. doi:10.1007/s12029-022-00906-z.
33. Brar G, Kasi PM. The utility of ctDNA in rectal cancer. Oncologist. 2025;30(11):oyaf354. doi:10.1093/oncolo/oyaf354.
34. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835–844. doi:10.1016/S1470-2045(10)70172-8.
35. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. 2019;5(4):e185896. doi:10.1001/jamaoncol.2018.5896.
36. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546–2556. doi:10.1200/JCO.22.00032.