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# Predictive Biomarkers and Models for Response to Total Neoadjuvant Therapy in Rectal Cancer: A Comprehensive Review

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## ABSTRACT

**Background:** The treatment of locally advanced rectal cancer (LARC) has been transformed by the implementation of Total Neoadjuvant Therapy (TNT), an intensive preoperative regimen that administers all planned chemotherapy and radiotherapy before surgery is considered. This approach has significantly raised the rates of pathological complete response (pCR), enabling organ preservation through a "watch-and-wait" (W&W) strategy for certain patients. The effectiveness of W & W critically depends on accurately identifying those who have achieved pCR without invasive procedures.

**Objective:** This review summarizes the latest evidence on predictive markers for response to TNT, examining both established and new methods such as clinical evaluations, advanced imaging techniques (including morphological and functional MRI, PET/CT), endoscopic assessments, and emerging molecular biomarkers like circulating tumor DNA (ctDNA) and genomic signatures from tissue samples. **Methods:** We searched PubMed, Google Scholar, and Science Direct for Rectal cancer, Total neoadjuvant therapy, Pathological complete response, Watch-and-Wait, Predictive biomarkers, MRI AND Circulating tumor DNA. Only the most recent or thorough investigation, from 2004 to 2025 was taken into account. The writers evaluated relevant literature references as well. Documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts were excluded.

**Conclusion:** Combining imaging, molecular diagnostics, and potentially artificial intelligence provides the most promising approach for selecting rectal cancer patients suitable for organ-preserving treatments, allowing for more tailored and effective care.

**Keywords:** Rectal cancer, Total neoadjuvant therapy, Pathological complete response, Watch-and-Wait, Predictive biomarkers, MRI, Circulating tumor DNA.

## INTRODUCTION

Rectal cancer continues to pose a major health problem worldwide. Traditionally, the standard treatment for locally advanced rectal cancer (LARC)—characterized by clinical stage T3-4 or presence of lymph node involvement—has involved neoadjuvant chemoradiotherapy (nCRT), followed by total mesorectal excision (TME) surgery, and then adjuvant chemotherapy [1]. Although this three-step approach improved control of the tumor locally, the risk of distant metastases persisted, and many patients struggled to complete adjuvant chemotherapy due to complications after surgery. To overcome these limitations, total neoadjuvant therapy (TNT) was developed, which entails administering all intended radiotherapy and multi-agent systemic chemotherapy before surgical intervention [2]. TNT can be given in two primary ways: Starting with induction chemotherapy followed by neoadjuvant chemoradiotherapy (nCRT), or beginning with nCRT followed by consolidation chemotherapy. Major clinical trials like RAPIDO and PROSPECT have highlighted the advantages of TNT, including better disease-free survival and a remarkable doubling of the pathological complete response (pCR) rate, with as many as 28% of patients having no remaining tumor in their surgical specimens [3, 4]. Pathological complete response (pCR) strongly predicts favorable long-term cancer outcomes. The increased pCR rates observed with Total Neoadjuvant Therapy (TNT) have renewed enthusiasm for organ preservation approaches, commonly known as the "watch-and-wait" (W & W) strategy. In this approach, patients who showed a complete clinical response following TNT can potentially forgo major surgery and its associated risks—like permanent stomas and functional impairments—by undergoing careful surveillance through frequent imaging and endoscopic examinations [5].

The key difficulty lies in precisely detecting a complete tumor response without performing surgery, since mistakes can lead to tumor recurrence. Dependable prediction methods are essential to safely implement the Watch-and-Wait strategy. This review examines the existing clinical assessments, imaging techniques, molecular markers, and computational approaches used to predict response to Total Neoadjuvant Therapy (TNT).

## CLINICAL AND ENDOSCOPIC ASSESSMENT

After completing neoadjuvant treatment, a patient's response is assessed through a detailed clinical and endoscopic examination. This evaluation is typically scheduled for 8 to 12 weeks post-treatment to ensure the tumor had enough time to shrink as much as possible.

### 1- Digital rectal examination (DRE)



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The digital rectal exam (DRE) is an essential, though subjective, method of evaluation. A complete response to treatment is suggested if the rectal wall feels smooth and soft where the tumor used to be. In contrast, if the examiner feels any remaining bumps, hardened areas, or ulcers, it strongly indicates that the tumor has not been fully eliminated [6].

**2- Endoscopy with biopsy**

Endoscopy with high-resolution imaging allows for direct inspection of the former tumor site, where signs of clinical complete response (cCR) include a pale lining, visible small blood vessels (telangiectasias), and a flat scar without lumps or ulcers. Nevertheless, visual assessment by itself is not definitive. The primary issue is the unreliability of biopsies; although essential for confirming a cCR, they can miss small pockets of residual tumor due to sampling errors, leading to a false-negative rate of 10–30%. This underscores the necessity of supplementary evaluation tools [7].

## IMAGING-BASED PREDICTION

Radiological imaging is the cornerstone of restaging after TNT [8].

**1- Magnetic resonance imaging (MRI)**

MRI provides exceptional soft tissue contrast, allowing detailed anatomical evaluation of the rectal wall and mesorectum [8].

The standard restaging MRI uses high-resolution T2-weighted (T2W) sequences to identify any remaining tumor. On these images, tumor regression is characterized by a decrease in tumor size and its replacement with low-signal scar tissue. The MRI tumor regression grade (mrTRG) system was developed to standardize this assessment, with lower scores (1–2) indicating a greater likelihood of a complete response. Key limitations, however, are the difficulty in differentiating residual tumor from post-treatment tissue changes and the lack of consistency between different interpreters [9].

Diffusion-weighted imaging (DWI) is a functional MRI technique that assesses therapeutic efficacy by measuring water diffusion. An increase in the apparent diffusion coefficient (ADC) post-treatment reflects a reduction in tumor cellularity, which is a strong predictor of a complete response. For this reason, DWI is now an indispensable component of MRI protocols when evaluating for a pathological complete response (pCR) [10].

**2- Positron emission tomography with computed tomography (PET/CT)**

A PET scan provides a quantitative measure of a tumor's metabolic activity, where a complete absence of FDG uptake is a strong predictor of a pathological complete response (pCR). Although suboptimal for local staging alone, PET is valuable for clarifying equivocal MRI results and is critical for detecting distant metastases before initiating a Watch-and-Wait protocol. Furthermore, hybrid PET/MRI technology may improve diagnostic accuracy by integrating functional and morphological data in a single session [11].

## MOLECULAR AND BIOMARKER-BASED PREDICTION

The frontier of response prediction lies in molecular biology. Biomarkers derived from blood or tumor tissue have the potential to provide highly specific and objective information, complementing clinical and radiological findings.

**1- Liquid biopsy: Circulating tumor DNA (ctDNA)**

Circulating tumor DNA (ctDNA) refers to DNA fragments shed by tumors into the bloodstream, acting as a non-invasive, real-time genomic marker. It is an emerging tool in rectal cancer with significant promise for predicting response to total neoadjuvant therapy (TNT). The underlying principle is that the presence of ctDNA indicates residual disease, while its clearance suggests a complete response. This has been validated by prospective studies, such as the CIRCULATE-Japan trial, which demonstrate that post-treatment ctDNA status is a powerful predictor of both pathological complete response (pCR) and future recurrence [12].

Patients who are ctDNA-negative after TNT have a very high likelihood of having achieved a pCR and demonstrate excellent long-term survival [13].

**2- Tissue-based genomic and transcriptomic markers**

Analysis of the initial diagnostic biopsy tissue can yield predictive information. Genomic markers, such as mutations in critical signaling pathways, can predict therapeutic resistance. For instance, KRAS mutations are known to mediate resistance to anti-EGFR agents and are also correlated with poorer clinical outcomes following standard chemoradiation [14]. While its role in TNT is still being elucidated, baseline mutational status (KRAS, BRAF, TP53) is likely to contribute to predictive models.

Microsatellite Instability (MSI): Approximately 3-5 % of locally advanced rectal cancers are characterized by high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR). Tumors with this profile demonstrate poor responses to conventional chemotherapy but have an exceptionally high sensitivity to immune checkpoint inhibitors. Although this status doesn't predict the outcome of standard neoadjuvant therapy, identifying it at diagnosis is critical, as it provides an opportunity to

use alternative and highly effective neoadjuvant treatments [15].

**3- Radiomics and artificial intelligence (AI)**

Radiomics is a technique that uses AI to find and analyze subtle details in medical images, like MRIs, that the human eye can't see. By studying these details, AI models can predict how well a tumor will respond to treatment before it even begins. While, this technology is still being developed, it has great promise for providing a more accurate and unbiased way to forecast patient outcomes [16].

## A MULTIMODAL INTEGRATED APPROACH

To make the best decisions in the future, doctors will combine information from many different tests. A possible step-by-step process for deciding if a patient can safely skip surgery ("Watch-and-Wait") might look like this, before treatment: The patient has detailed MRI scans, a special blood test for cancer DNA (ctDNA), and a biopsy to check the tumor's genetic profile. After treatment: The patient undergoes a physical exam, a camera inspection (endoscopy), another MRI, and a repeat of the ctDNA blood test. Making the decision: A patient is an ideal candidate for "Watch-and-Wait" only if they pass every test, showing a deep and complete response. This means there is no tumor found on the physical exam or endoscopy, the MRI results are excellent, and most importantly the cancer DNA is completely gone from their blood.

This combined approach uses imaging, blood tests, and direct observation to be as confident as possible that the cancer is truly gone.

## CONCLUSION AND FUTURE DIRECTIONS

Total Neoadjuvant Therapy (TNT) has become a game-changer in rectal cancer treatment, helping more people avoid surgery and keep their organs. The biggest challenge is accurately predicting which tumors will disappear completely. Thankfully, new technologies like "liquid biopsies" (using ctDNA) and advanced AI imaging are being developed to provide a clearer, more personalized prediction. With major studies like the OPRA trial underway, we expect to soon have reliable and combined methods to safely guide "Watch-and-Wait" decisions, leading to better outcomes and fewer side effects.

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