Interpretation of Key Updates in the 2024 V1/V2 Edition of the NCCN Guidelines for Rectal Cancer (Postprint)

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Abstract

Colorectal cancer (CRC) ranks as the second most common cancer in China and represents one of the frequent malignant tumors of the digestive system. With advancing medical research and technological progress, its diagnostic and therapeutic strategies continue to evolve. The National Comprehensive Cancer Network (NCCN), staying abreast of scientific frontiers, released the 2024 V1/V2 editions of the NCCN Clinical Practice Guidelines for Rectal Cancer on January 29, 2024, and April 4, 2024, respectively. These revisions primarily concentrate on recent developments in molecular testing, immunotherapy, targeted therapy, neoadjuvant therapy, and disease monitoring. By analyzing the key updates in the 2024 V1/V2 NCCN guidelines, this article seeks to furnish more precise reference points for clinical practice in the diagnosis and treatment of rectal cancer.

Full Text

Interpretation of Key Updates in the 2024 V1/V2 NCCN Clinical Practice Guidelines for Rectal Cancer

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Abstract

Colorectal cancer (CRC) ranks as the second most common cancer in China and represents one of the most frequent malignant tumors of the digestive system. As medical research advances and technology evolves, diagnostic and therapeutic strategies for CRC continue to develop. The National Comprehensive Cancer Network (NCCN), staying at the forefront of scientific progress, released the 2024 V1/V2 versions of the NCCN Clinical Practice Guidelines for Rectal Cancer on January 29 and April 4, 2024, respectively. These revisions primarily focus on the latest advances in molecular detection, immunotherapy, targeted therapy, neoadjuvant therapy, and disease surveillance. This article analyzes the key updates in the 2024 V1/V2 NCCN guidelines to provide more precise reference points for clinical diagnosis and treatment of rectal cancer.

Keywords: Rectal neoplasms; Mutation testing; Treatment strategy; Surveillance; NCCN; Guidelines interpretation

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According to 2022 data estimates, approximately 517,100 new colorectal cancer cases occurred in China, accounting for 10.7% of all new malignant tumor cases. Colorectal cancer represents a major cause of cancer mortality in both men and women [1]. Rectal cancer, a subset of colorectal cancer, is among the most common malignant tumors of the digestive tract. Although overall incidence has declined due to advances in screening technology, rates are rising in younger populations—a trend that has attracted significant concern. Moreover, rectal cancer patients are often diagnosed at more advanced stages, resulting in greater treatment complexity and poorer prognosis. Consequently, interpretation of NCCN guideline updates proves particularly critical.

The 2024 V1/V2 NCCN Clinical Practice Guidelines for Rectal Cancer (hereinafter referred to as the NCCN Guidelines) introduce substantial updates in molecular detection, treatment regimens, and disease monitoring, injecting new momentum into precision medicine for rectal cancer. These updates emphasize next-generation sequencing (NGS) testing, molecular detection, precision targeted therapy, immunotherapy, neoadjuvant treatment strategies, and post-treatment surveillance, aiming to improve therapeutic efficacy and patient quality of life. Notably, the NCCN Guidelines place DNA polymerase catalytic subunit gene/DNA polymerase $ $1 catalytic subunit gene (POLE/POLD1) mutations on par with mismatch repair deficiency/microsatellite instability-high (dMMR/MSI-H) testing throughout the guidelines, a move that expands the eligible population for immunotherapy and offers hope to more patients. While these updates provide valuable references for rectal cancer diagnosis and treatment in China, their application must carefully consider the influence of ethnic and racial differences in incidence and mortality rates across populations [2].

This article provides a detailed interpretation of the NCCN guideline updates from the perspectives of rectal cancer detection, treatment, and surveillance.

1. Molecular Testing Principles

1.1 General Principles

Molecular testing provides indispensable diagnostic information for rectal cancer by detecting genetic and protein alterations in tumor cells. The 2024 V1 NCCN Guidelines include several revisions in this domain, addressing two key aspects of comprehensive molecular testing application. First, re-genotyping should be performed after targeted therapy. Targeted therapies directed against specific gene mutations or molecular pathways can induce genomic changes in tumors and cause new mutations, leading to drug resistance [3]. Therefore, repeat genetic testing after targeted therapy helps identify novel mutations and understand tumor response mechanisms and potential resistance patterns. Second, repeat molecular testing is not recommended after standard cytotoxic chemotherapy. Unlike targeted therapy, cytotoxic chemotherapy acts through a different mechanism that minimally impacts gene mutations, primarily killing rapidly dividing cells rather than directly targeting specific genetic alterations or molecular pathways.

1.2 POLE/POLD1 Mutations

For suspected or confirmed distant metastatic rectal cancer, the new guidelines adjust molecular testing requirements beyond conventional detection of rat sarcoma oncogene (RAS) and B-Raf oncogene (BRAF) mutations, human epidermal growth factor receptor 2 (HER2) amplification, and mismatch repair (MMR) or microsatellite instability (MSI) status. The updated guidelines now include screening for rare driver mutations and gene fusions: POLE/POLD1 mutations, rearranged during transfection (RET) fusions, and neurotrophic receptor tyrosine kinase (NTRK) fusions. Although these rare molecular alterations occur at low frequency, they carry significant therapeutic implications. The NCCN Guidelines specifically highlight two polymerase-related gene variants—POLE and POLD1—and assign them equal importance with dMMR/MSI-H in metastatic colorectal cancer (mCRC) patients.

The POLE and POLD1 genes encode proteins responsible for recognizing and correcting errors during DNA replication, thereby maintaining accurate genetic information transmission. However, pathogenic variants in these genes disable their proofreading function [4], leading to massive accumulation of mutations within cells. In clinical observations of metastatic rectal cancer, patients harboring POLE/POLD1 mutations are relatively rare, predominantly appearing in those with mismatch repair proficient/microsatellite stable (pMMR/MSS) phenotypes [5], with an overall incidence of approximately 7.37%. Despite their rarity, these patients exhibit significantly higher tumor mutation burden (TMB) than non-mutated patients [6], resulting in increased neoantigen generation and effective activation of anti-tumor immune responses. Notably, although POLE/POLD1 mutations differ mechanistically from dMMR/MSI-H phenotypes, they demonstrate similarity in triggering high TMB and neoantigen

production [7], providing a theoretical foundation for treating POLE/POLD1-mutated rectal cancer patients with immune checkpoint inhibitors and suggesting potential for favorable treatment responses.

1.3 Molecular Testing Modalities

The NCCN Guidelines designate NGS as the preferred molecular testing method, recommending that all metastatic rectal cancer patients undergo NGS-based genotyping for RAS and BRAF mutations. The guidelines emphasize the importance of broad gene panel testing, as NGS can simultaneously detect targets ranging from tens of thousands of genes to small panels [8], enabling timely identification of numerous rare targets in clinical practice to more precisely guide subsequent colorectal cancer treatment.

In oncology, circulating tumor DNA (ctDNA) has emerged as an innovative biomarker attracting increasing attention due to its potential value in monitoring tumor burden and predicting treatment response and disease progression. A recent meta-analysis examining ctDNA detection in 1,676 locally advanced rectal cancer patients across 22 studies revealed that ctDNA positivity directly correlates with significantly increased recurrence risk [9]. Notably, this risk elevation is particularly pronounced in patients tested after neoadjuvant therapy or surgery. Specifically, ctDNA-positive patients after neoadjuvant therapy face nearly ninefold higher recurrence risk (hazard ratio = 8.87), while postoperative ctDNA positivity confers a staggering 15-fold increased risk (hazard ratio = 15.15). These findings further confirm ctDNA's important prognostic role in locally advanced rectal cancer and provide solid scientific evidence for its application as a prognostic biomarker.

Despite ctDNA's promising potential in predicting rectal cancer prognosis, current evidence remains insufficient to support its widespread adoption in routine clinical practice. The field requires further research to validate ctDNA's practical clinical value, particularly in determining treatment regimens and adjusting therapeutic doses. Consequently, the NCCN Guidelines advise cautious consideration when incorporating ctDNA testing into future clinical decision-making to avoid premature treatment adjustments based on ctDNA results.

2. Treatment Strategies

2.1 Surgical Treatment

The latest guideline revisions introduce both non-surgical and surgical pathways for T1, N0 stage rectal cancer patients, providing more precise treatment options. For resectable cases, the NCCN Guidelines newly include endoscopic submucosal dissection (ESD) as a treatment option and expand the description of ESD's role.

Surgical resection remains the preferred treatment for non-metastatic rectal cancer. For early-stage disease (such as T1 or T2, N0), particularly T1a tumors

confined to the submucosa, local excision procedures like endoscopic mucosal resection or ESD represent viable treatment alternatives. ESD is a minimally invasive, organ-preserving technique that enables en bloc resection of early rectal cancer lesions through submucosal injection and dissection, achieving radical excision. Additionally, ESD facilitates accurate pathological staging even when radical resection is not performed.

The newly added ESD content emphasizes its advantages in achieving complete full-thickness resection through an endoscopic approach, thereby avoiding trauma associated with conventional surgery. Compared with transanal endoscopic microsurgery (TEM), ESD demonstrates superior safety while shortening hospitalization duration, with no significant differences in en bloc resection rates, technical success rates, or tumor recurrence rates [10].

2.2 Neoadjuvant Therapy for pMMR/MSS

For pMMR/MSS patients with synchronous liver and/or lung metastases (resectable), the NCCN Guidelines delineate two treatment pathways: (1) chemotherapy (with optional radiation) and (2) chemotherapy plus radiation. The specific pathways are illustrated in Figure 1 [Figure 1: see original paper].

According to five-year follow-up results from an international multicenter phase III clinical study, patients receiving short-course radiation followed by chemotherapy and surgery demonstrated a 10% locoregional recurrence rate, significantly higher than the 6% observed in the control group receiving chemotherapy followed by surgery and adjuvant chemotherapy [11]. This indicates that short-course radiation combined with chemotherapy increases the likelihood of local recurrence and treatment failure in colorectal cancer. Therefore, for pMMR/MSS patients, particularly those with advanced or metastatic rectal cancer, the NCCN Guidelines recommend chemotherapy followed by surgical resection as the preferred approach, no longer considering radiation a necessary component.

2.3 Targeted Therapy

2.3.1 Anti-Epidermal Growth Factor Receptor (EGFR) Therapy For pMMR/MSS patients with synchronous liver and/or lung metastases (unresectable) or those medically unfit for surgery, the NCCN Guidelines add that patients with BRAF mutations other than V600E may consider anti-EGFR therapy. Clinical research confirms that BRAF V600E mutation represents the only known class 1 BRAF mutation that cannot provide feedback inhibition of RAS pathway activation, causing aberrant pathway activation that renders single-agent anti-EGFR therapy ineffective and requires combination with BRAF and MEK inhibitors to improve efficacy. TAN et al. [12] investigated combined BRAF inhibitor (vemurafenib) and EGFR inhibitor (erlotinib) therapy in BRAF V600E-mutated mCRC, demonstrating significantly improved progression-free survival (PFS) and overall survival (OS), indicating that combination therapy

is superior to single-agent anti-EGFR treatment for BRAF V600E-mutated patients.

Previous research and clinical trials have primarily focused on BRAF V600E mutations, with relatively limited data on other mutations. The clinical benefit of EGFR monoclonal antibodies in rectal cancer patients with non-V600E BRAF mutations remains inadequately studied. Future randomized controlled trials targeting this specific mutation type are needed to clarify the therapeutic efficacy of EGFR monoclonal antibodies in these patients.

2.3.2 Anti-HER2 Therapy The 2024 V1 NCCN Guidelines updated recommendations for trastuzumab deruxtecan (T-DXd), removing restrictions on RAS and BRAF status and limiting indications to "HER2 amplification" at a recommended dose of 5.4 mg/kg every 21 days. The 2024 V2 guidelines further added immunohistochemistry (IHC) restrictions, implementing stricter diagnostic criteria for HER2-amplified patients by modifying T-DXd indications to "HER2 amplification (IHC3+)."

This update is primarily treatment-based. The 2023 v6 NCCN guidelines considered anti-HER2 therapy ineffective regardless of HER2 expression when RAS/BRAF mutations were detected in ctDNA, rendering HER2 status testing meaningless. However, the recent DESTINY-CRC02 study demonstrated significant anti-tumor activity of T-DXd in HER2-positive metastatic rectal cancer patients irrespective of RAS/BRAF mutation status. Unlike earlier studies (HERACLES-B, TRIMUPH, and MOUNTAINEER) that only included RAS/BRAF wild-type mCRC patients, DESTINY-CRC02 did not exclude RAS/BRAF-mutated patients. The study showed an objective response rate (ORR) of 28.6% in mutated patients, lower than the 39.7% in wild-type patients, but still confirming efficacy. Therefore, RAS/BRAF mutation status is no longer a restriction for T-DXd use in anti-HER2 therapy for metastatic rectal cancer.

As an antibody-drug conjugate (ADC), T-DXd combines a small molecule drug with a monoclonal antibody to kill tumor cells. However, anti-HER2 therapy combining signal transcription inhibition remains limited to HER2-amplified patients with RAS/BRAF wild-type status. Biomarker-directed therapy options are detailed in Table 1 .

The DESTINY-CRC02 trial also compared two T-DXd doses (5.4 mg/kg vs 6.4 mg/kg) for efficacy and safety. Previous studies found that higher T-DXd doses could cause interstitial lung disease, with DESTINY-CRC01 reporting 3.5% mortality from pulmonary toxicity [13]. The latest results showed no significant differences in PFS or OS between the two doses, but the 5.4 mg/kg group achieved superior ORR (37.8% vs 27.5%) with no grade 5 interstitial pneumonia-related deaths, demonstrating better safety and efficacy at the lower dose.

Unlike breast and gastric cancers, HER2-positive diagnosis in rectal cancer is

particularly complex. According to HERACLES diagnostic criteria, HER2 positivity determination requires combined IHC and in situ hybridization (ISH) testing [14]. IHC2+ or lower results mandate further fluorescence in situ hybridization (FISH) testing to confirm HER2 gene amplification. IHC3+ represents one diagnostic criterion for HER2 positivity, defined as strong membrane staining in over 50% of tumor cells, which carries significant implications for subsequent treatment selection. Previous studies found that T-DXd did not improve efficacy in patients with lower HER2 expression levels (IHC2+, IHC1+) [13]. Therefore, the 2024 V2 NCCN guidelines combine HER2 amplification and IHC3+ criteria as T-DXd indications to ensure the drug targets patients most likely to benefit.

Although anti-HER2 targeted therapy is widely used in breast and gastric cancers [15], HER2 amplification occurs in only a small percentage of mCRC patients [16], suggesting that treatment advances may progress more gradually. We anticipate that future targeted therapeutic agents will play a greater role in the comprehensive treatment of rectal cancer.

2.4 Immunotherapy

Current cancer treatment, including colorectal cancer, has entered the immunotherapy era. Clinical evidence confirms that immune checkpoint inhibitor-based monotherapy or combination regimens significantly improve patient outcomes. However, for rectal cancer patients, the proportion who respond to immunotherapy remains extremely low. Among all rectal cancer patients, the currently recognized optimal immunotherapy beneficiaries are dMMR/MSI-H patients, who represent only approximately 5% of cases [17]. The NCCN guideline update placing POLE/POLD1 mutations on par with dMMR/MSI-H in metastatic tumor stratification aims to further expand the immunotherapy-eligible population.

Concurrently, the NCCN Guidelines provide treatment options for dMMR/MSI-H or POLE/POLD1-mutated patients who cannot receive checkpoint inhibitors due to various reasons (drug intolerance, comorbidities, etc.). For patients with contraindications to immune checkpoint inhibitors, neoadjuvant chemotherapy with FOLFOX (leucovorin + fluorouracil + oxaliplatin), CAPEOX (capecitabine + oxaliplatin), or FOLFIRINOX (leucovorin + fluorouracil + irinotecan + oxaliplatin) is recommended, followed by re-evaluation and subsequent treatment steps similar to patients receiving immune checkpoint inhibitors.

In a recent study, ANDRÉ et al. [18] randomized 307 previously untreated dMMR/MSI-H mCRC patients 1:1 to receive pembrolizumab or chemotherapy. Results showed that although the pembrolizumab group achieved significantly prolonged PFS, mortality rates were similar between the pembrolizumab (56 cases) and chemotherapy (69 cases) groups. Notably, immune checkpoint inhibitors carry higher risks of early progression compared to chemotherapy, while

neoadjuvant chemotherapy regimens have demonstrated low risk and significant efficacy across multiple cancer types, providing an effective alternative for patients unsuitable for immunotherapy.

3. Post-Treatment Surveillance and Management

Post-treatment surveillance and management constitute crucial components of patient care. The NCCN Guidelines propose a series of optimized surveillance strategies to improve patient outcomes and quality of life. For surgically treated patients, the guidelines add specific monitoring protocols following low-risk polypectomy, recommending physical examination and rectoscopy every 3–6 months during the first two years post-procedure, with colonoscopy performed at one year after surgery.

For patients receiving non-surgical treatment, the NCCN Guidelines shorten the surveillance duration for rectal MRI from "every 6 months for at least 3 years" to "for 3 years." This modification is based on analysis of clinical data and trial results showing that most cancer recurrences occur within the first 3–5 years [19], making regular surveillance most effective during this period. Furthermore, more frequent monitoring has not demonstrated significantly improved survival rates [20] while increasing patient burden. Therefore, the NCCN Guidelines specify a 3-year surveillance period and recommend colonoscopic monitoring for stage IV patients with clinical complete response after non-surgical treatment, starting from the first documented complete response to enable early detection of any potential recurrence and intervention at a controllable stage, thereby improving prognosis.

4. Conclusion

Colorectal cancer represents an indispensable component of general practice. Understanding the latest NCCN guideline research findings helps physicians better manage colorectal cancer patients—China's second most common malignancy. The NCCN Guidelines provide essential guidance for early identification of rectal cancer signs and symptoms, enabling more accurate identification of high-risk populations and targeted prevention and screening recommendations to facilitate early diagnosis. The guidelines also emphasize the importance of multidisciplinary collaboration in developing tailored treatment plans while promptly detecting and managing recurrence or metastasis and enhancing patient education.

These two NCCN guideline updates integrate the latest scientific advances, providing rectal cancer patients with more comprehensive testing options and treatment guidance. The guidelines further refine targeted therapy directives, expand the immunotherapy-eligible population, and standardize post-treatment surveillance timing. These updates not only enhance the accuracy of early rectal cancer diagnosis but also further standardize treatment strategies, aiming to improve therapeutic outcomes and prognosis for rectal cancer patients.

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Note: Figure translations are in progress. See original paper for figures.