

Review

Nodal Staging and Response Assessment in Locally Advanced Mismatch Repair–Deficient Colon and Rectal Cancer in the Era of Neoadjuvant Immune Checkpoint Inhibitors

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Abstract

Mismatch repair–deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancers exhibit high mutational burden and abundant neoantigen formation, generating a highly immunogenic tumour microenvironment characterised by dense lymphocytic infiltration and strong sensitivity to immune checkpoint inhibition. In metastatic colorectal cancer, PD-1 blockade produces durable responses almost exclusively in dMMR tumours, establishing mismatch repair status as a predictive biomarker for immunotherapy responsiveness. Recent studies extending immune checkpoint inhibitors (ICIs) into the neoadjuvant setting for localised dMMR colorectal cancer have produced major pathological response rates exceeding 90%, with pathological complete response (pCR) rates frequently surpassing 60%, challenging traditional oncologic staging frameworks, particularly with respect to lymph node assessment. Baseline clinical nodal staging in dMMR tumours is complicated by immune-mediated lymphadenopathy. Reactive lymphoid hyperplasia driven by tumour antigen exposure frequently produces enlarged lymph nodes that mimic metastatic disease on cross-sectional imaging. Following neoadjuvant immunotherapy, treatment-related immune activation may further increase nodal size or metabolic activity, while pathological examination often reveals sterilised nodes or immune infiltration without viable tumour. Consequently, conventional radiologic criteria for nodal metastasis demonstrate limited specificity in this context. The discordance between imaging findings and pathological outcomes raises important implications for staging accuracy, response assessment, and treatment planning. This review examines the biological basis of lymphatic involvement in dMMR colorectal cancer, evaluates the performance of current imaging modalities for nodal staging, and summarises emerging evidence from neoadjuvant immunotherapy trials. Particular emphasis is placed on the interpretation of lymph node findings in the era of immune checkpoint blockade and the implications for surgical decision-making, organ preservation, and future staging paradigms.



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Keywords: mismatch repair deficiency; microsatellite instability; colorectal cancer; immune checkpoint inhibitors; neoadjuvant immunotherapy; nodal staging; lymph node; tumour-draining lymph nodes; pathological response

1. Introduction

Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer represents a biologically distinct molecular subtype, accounting for approximately 15% of non-metastatic colon cancers [1,2]. These tumours arise from defects in the DNA mismatch repair system, most commonly involving MLH1, MSH2, MSH6, or PMS2, impairing correction of base–base mismatches and insertion–deletion loops during DNA replication [3]. The resulting accumulation of replication errors preferentially affects microsatellite regions, producing the MSI-H phenotype and a hypermutated genomic landscape [1]. Identification of dMMR disease is typically performed through immunohistochemical assessment of mismatch repair protein expression or by PCR-based detection of MSI-H [1,3]. For the purposes of this review, we will refer to dMMR/MSI-H tumours interchangeably.

The genomic instability characteristic of dMMR tumours leads to an exceptionally high tumour mutational burden (TMB) and the generation of numerous neoantigens capable of stimulating adaptive immune responses [4,5]. Consequently, dMMR colorectal cancers frequently demonstrate a highly inflamed tumour microenvironment characterised by dense cytotoxic CD8⁺ T-cell infiltration, Th1-polarised cytokine signalling, and upregulation of immune checkpoint molecules including PD-1, PD-L1, and CTLA-4 [4–9]. These immunologic features underpin the remarkable sensitivity of dMMR colorectal cancer to immune checkpoint inhibitors (ICIs).

In metastatic disease, PD-1 blockade produces durable responses almost exclusively in dMMR tumours, establishing mismatch repair status as a predictive biomarker for immunotherapy efficacy [1,5,10]. The extension of checkpoint inhibition into more locally advanced but earlier stage disease has produced unprecedented response rates in resectable dMMR colorectal cancer, particularly in the neoadjuvant setting, with major pathological response rates exceeding 90% and pathologic complete response (pCR) rates frequently exceeding 60% [11–13]. These extraordinary results raise important questions regarding the interpretation of response in both the primary and the locoregional tumour-draining lymph nodes (TDLNs).

Lymph node status has historically been central to colorectal cancer staging and treatment planning. However, the immunogenic biology of dMMR tumours complicates conventional nodal staging. Reactive lymphadenopathy driven by immune activation may mimic nodal metastases at baseline, while immune-mediated tumour regression after checkpoint blockade may produce persistent structural abnormalities within lymph nodes despite eradication of viable tumour cells. Critically, TDLNs are not only sites of metastatic dissemination but also key immunologic organs, primary sites of antigen presentation and T-cell priming, that link lymphatic biology directly to the mechanism of action of immune checkpoint inhibition. The interaction between tumour biology, lymphatic immune function, and checkpoint blockade therefore introduces new complexities in nodal staging and response assessment. This review examines the biological mechanisms, clinical evidence, and current limitations of nodal staging and response assessment in resectable dMMR colon and rectal cancer treated with neoadjuvant ICIs, with particular emphasis on lymph node immunobiology, patterns of nodal regression after immunotherapy, and the implications for imaging interpretation, surgical management, and organ preservation strategies.

Scope and Search Strategy

This narrative review was informed by a structured search of PubMed, Scopus, Web of Science, and the Cochrane Library for articles pertaining to neoadjuvant immune checkpoint inhibition in colorectal cancer, conducted from database inception to the final search date of 28 February 2026. Controlled vocabulary and free-text terms were combined using

the Boolean operators AND and OR, broadly structured as (“mismatch repair deficiency” OR “microsatellite instability” OR dMMR OR MSI) AND (“colorectal cancer” OR “colon cancer” OR “rectal cancer”) AND (“immune checkpoint inhibitor” OR immunotherapy OR neoadjuvant) AND (“lymph node” OR “nodal staging” OR “pathological response”); reference lists of retrieved articles and pertinent reviews were hand-searched to identify additional sources. Given the rapidly evolving evidence base and the predominance of early-phase and emerging data in this field, conference abstracts and other reports not yet subject to full peer review were included where they contributed unique or contemporaneous data not otherwise available, and such sources are identified as conference abstracts and interpreted with appropriate caution. No formal quality appraisal or quantitative synthesis was undertaken, consistent with the narrative scope of the review.

2. Biological Basis of Immune Sensitivity and Lymph Node Response in dMMR Colorectal Cancer

2.1. Neoantigen Generation and the Tumour Immune Microenvironment

dMMR represents one of the clearest examples in oncology in which tumour genotype directly shapes the immunologic phenotype. Frameshift mutations arising within coding regions generate altered proteins containing novel peptide sequences that are processed through MHC pathways as neoantigens recognised by the adaptive immune system [4,5,14]. As a result, dMMR colorectal cancers demonstrate a highly inflamed tumour microenvironment characterised by abundant cytotoxic CD8⁺ T lymphocytes, Th1-polarised cytokine signalling, and upregulation of PD-1, PD-L1, and CTLA-4 [4–9]. In many cases these tumours exist in a state of immune equilibrium in which endogenous antitumour immunity is present but restrained by inhibitory checkpoint signalling, the biological rationale for the dramatic responses seen following checkpoint blockade (Figure 1).

While dMMR tumours are typically enriched for Tc1 and Th1 lymphocyte populations and relatively depleted of regulatory T cells and Th2 subsets, producing a pro-inflammatory milieu conducive to cytotoxic antitumour activity, there can be substantial heterogeneity between tumours [15]. Densities of CD3⁺ and CD8⁺ tumour-infiltrating lymphocytes can vary considerably among dMMR tumours, and a subset exhibits immune infiltration comparable to microsatellite-stable cancers, which may partly explain differential responsiveness to checkpoint blockade observed across patients [16,17]. Innate immune sensing pathways further shape this environment. cGAS-STING pathway activation promotes lymphocyte recruitment through CXCL10 and CCL5 induction [18] while heightened interferon- γ responsiveness induces PD-L1 expression via JAK-STAT signalling [19,20]. Alterations affecting this pathway, including JAK1 frameshift mutations, present in approximately 20% of MSI-H colorectal cancers, are associated with reduced interferon response signatures and resistance to PD-1 blockade, and are discussed in more detail in Section 2.5 [21–23].

Another important feature of the dMMR immune landscape is the presence of tertiary lymphoid structures (TLS) (Figure 2). These ectopic lymphoid aggregates resemble secondary lymphoid organs and arise within chronically inflamed tumour tissue, containing organised B-cell follicles surrounded by T cells, dendritic cells, macrophages, and high endothelial venules that facilitate lymphocyte trafficking [24,25]. dMMR colorectal cancers demonstrate higher TLS density than mismatch repair-proficient tumours, and the presence of intratumour TLS has been associated with improved responses to PD-1 blockade [26]. MSI colorectal cancers also demonstrate increased spatial interactions between Th1, Tc1, and dendritic cells compared with microsatellite-stable tumours, further underscoring the coordinated immune architecture that may sustain effective antitumour immunity during checkpoint inhibition [15].

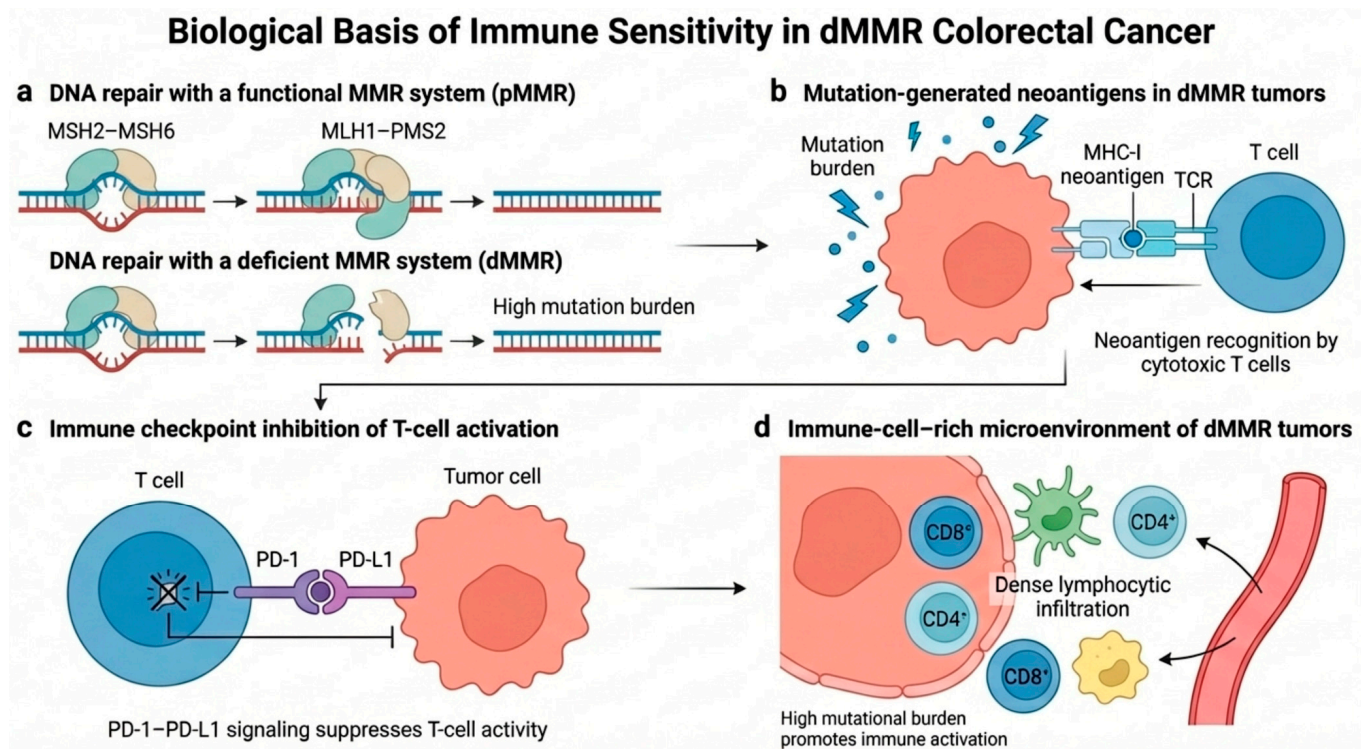


Figure 1. Biological basis of immune sensitivity in dMMR colorectal cancer. (a) In normal cells, DNA replication errors are corrected by the mismatch repair (MMR) system through coordinated activity of the MLH1/PMS2 and MSH2/MSH6 protein complexes. (b) Loss of MMR function in dMMR/MSI-H tumours leads to accumulation of mutations and generation of neoantigens that are presented on tumour cells via MHC class I molecules and recognised by cytotoxic T cells. (c) Tumour immune responses can be suppressed through immune checkpoint signalling such as PD-1–PD-L1 interaction, which inhibits T-cell activation. (d) The high mutational burden of dMMR tumours produces an immune-cell-rich tumour microenvironment characterised by dense lymphocytic infiltration, which contributes to the marked sensitivity of these tumours to immune checkpoint inhibition. Created in <https://BioRender.com>.

The spatial organisation and density of immune infiltrates within dMMR tumours may be critical determinants of response to neoadjuvant immunotherapy. Tumours with coordinated interactions between dendritic cells, cytotoxic T cells, and helper T-cell populations appear more capable of sustaining effective antitumour immunity during checkpoint inhibition. Conversely, defects in antigen presentation pathways, including alterations affecting interferon signalling, may contribute to immune resistance in a subset of dMMR tumours [21,22]. These observations suggest that not all dMMR tumours are equally immunogenic and that the biological heterogeneity of the dMMR population has important implications for predicting responses to neoadjuvant ICI. Understanding which patients are most likely to achieve nodal sterilisation, and which may require intensified or alternative treatment strategies, remains a key challenge for the field.

2.2. TDLNs in Antitumour Immunity

TDLNs play a central role in orchestrating antitumour immune responses within the lymphatic system. These nodes function as the primary site where tumour-derived antigens are presented to naïve T cells, leading to activation and expansion of tumour-specific effector lymphocytes [27]. Antigen transport from tumours to regional lymph nodes is mediated largely by migratory CCR7⁺ dendritic cells, which deliver tumour antigens to lymph node-resident conventional dendritic cell type 1 (cDC1) populations [28]. These interactions prime tumour-specific CD8⁺ T cells and imprint homing programmes

that guide activated lymphocytes back to the tumour microenvironment. Checkpoint inhibition amplifies this process: PD-1 blockade promotes T-cell expansion within TDLNs and enhances trafficking of activated effector cells to tumour sites [29,30]. Experimental studies demonstrate that disruption of lymph node-mediated immune priming markedly reduces the efficacy of PD-1/PD-L1 blockade, underscoring the central role of TDLNs in mediating the therapeutic effects of ICIs [27]. In the immunotherapy context, lymph nodes therefore function not only as sites of metastatic dissemination but as immunologic organs actively participating in tumour eradication (Figure 3).

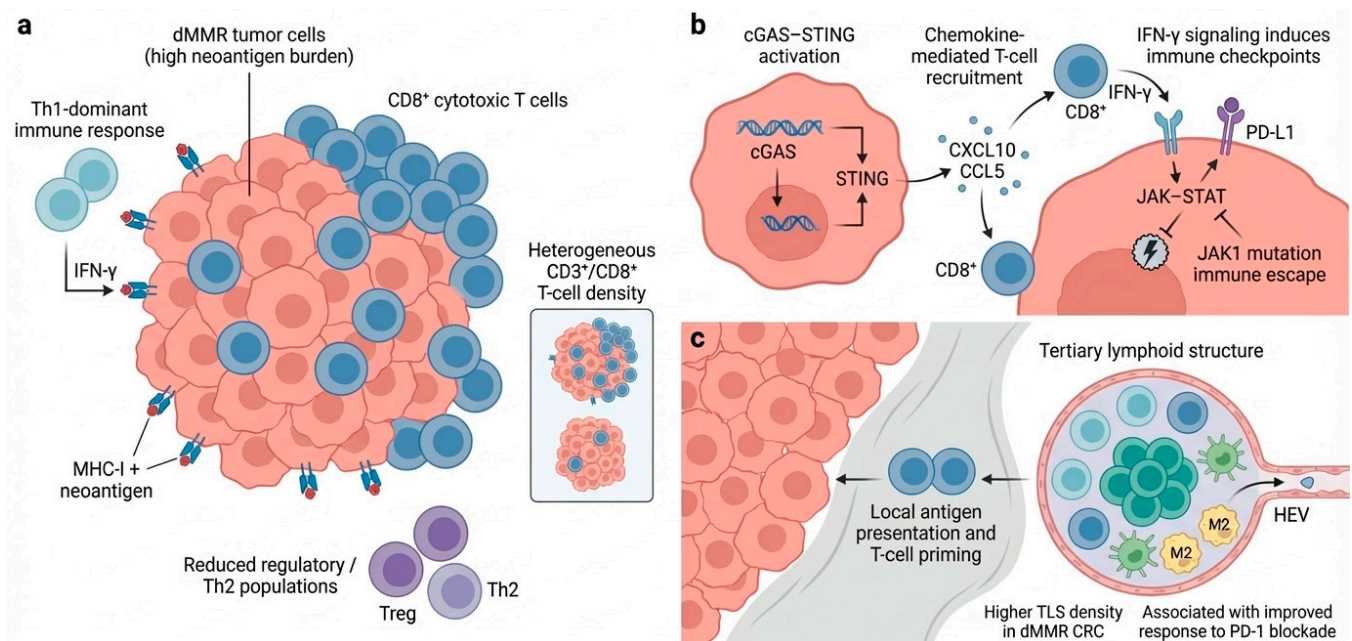


Figure 2. Immune microenvironment of dMMR colorectal cancer. (a) dMMR colorectal cancers exhibit a high neoantigen burden that promotes a Th1-dominant immune response characterised by infiltration of CD8⁺ cytotoxic T cells. Despite this generally inflamed phenotype, tumours demonstrate heterogeneity in CD3⁺ and CD8⁺ T-cell density, with relatively reduced regulatory T-cell and Th2 populations. (b) Innate immune sensing pathways contribute to immune activation. Activation of the cGAS–STING pathway induces chemokine production (e.g., CXCL10 and CCL5), promoting recruitment of tumour-infiltrating lymphocytes. Interferon-γ signalling through the JAK–STAT pathway further enhances immune responses but also induces immune checkpoint molecules such as PD-L1, while mutations affecting this pathway (e.g., JAK1) may facilitate immune escape. (c) dMMR tumours frequently contain TLS composed of organised B-cell follicles, T cells, dendritic cells, macrophages, and high endothelial venules (HEVs), which support local antigen presentation and T-cell priming. Increased TLS density has been associated with improved responses to PD-1 blockade. Created in <https://BioRender.com>.

2.3. The Neoadjuvant Platform and Lymphatic Biology

The neoadjuvant delivery of ICIs offers distinct biological and translational advantages over postoperative therapy. With the primary tumour in situ, the full neoantigen repertoire remains available for lymph node-based immune priming, promoting broader activation and expansion of tumour-specific T-cell clones and facilitating systemic immune memory capable of targeting micrometastatic disease [31–33]. In melanoma, neoadjuvant checkpoint inhibition induces greater expansion of tumour-reactive T-cell clones than adjuvant therapy and is associated with improved event-free survival [31,33]. Preclinical models demonstrate stronger systemic CD8⁺ T-cell responses and more effective micrometastatic eradication when checkpoint blockade is administered prior to tumour resection [34]. Administering ICIs while the tumour and its draining lymphatic network remain intact therefore allows ex-

pansion of tumour-specific T-cell populations within lymph nodes before surgical removal (Figure 4).

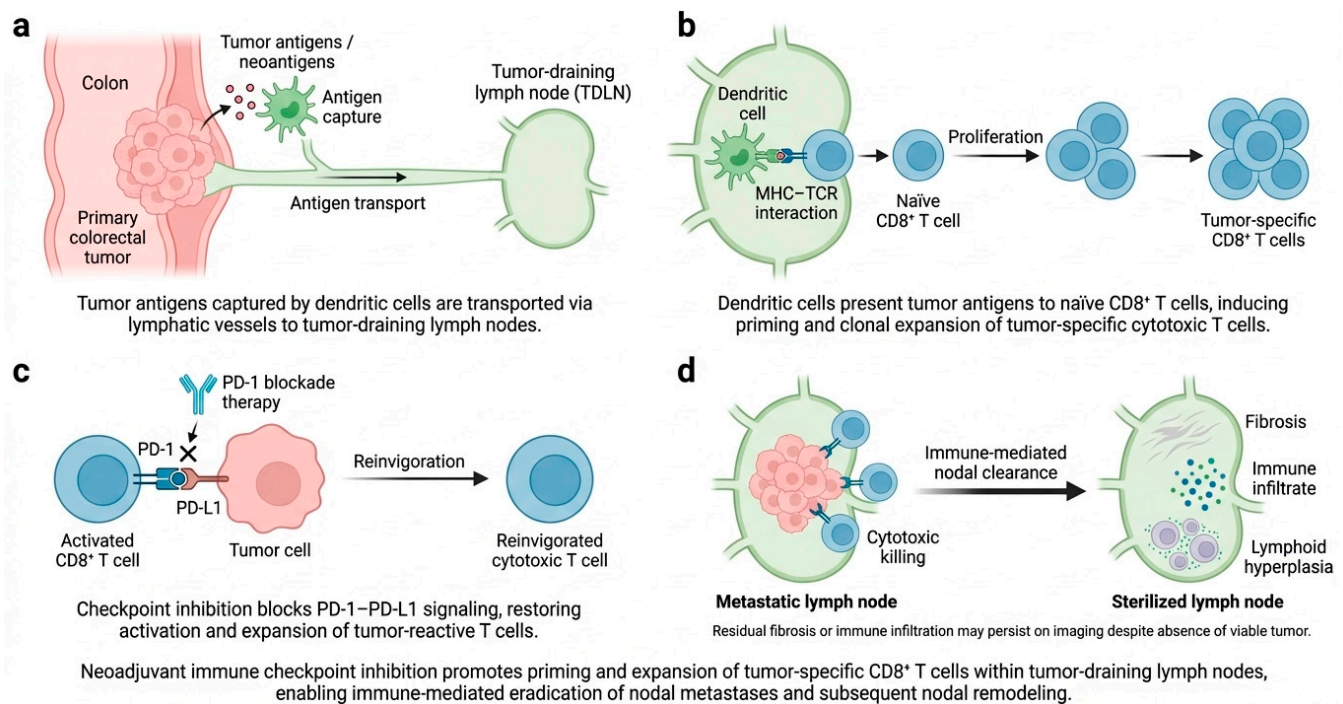


Figure 3. Mechanisms of nodal clearance following neoadjuvant immune checkpoint inhibition in dMMR colorectal cancer. (a) Tumour-derived neoantigens from the primary colorectal cancer are captured by antigen-presenting cells and transported via lymphatic vessels to tumour-draining lymph nodes. (b) Within the lymph node, dendritic cells present tumour antigens to naïve CD8⁺ T cells through MHC–T-cell receptor interactions, leading to priming and clonal expansion of tumour-specific cytotoxic T cells. (c) Immune checkpoint inhibition blocks suppressive signalling pathways such as PD-1–PD-L1, allowing reinvigoration and expansion of tumour-reactive T-cell populations that traffic to both the primary tumour and involved lymph nodes. (d) Activated cytotoxic T cells mediate immune destruction of tumour cells within lymph nodes, resulting in nodal sterilisation and immune-mediated remodelling characterised by lymphoid hyperplasia, fibrosis, and inflammatory infiltrates, changes that may persist radiologically despite absence of viable tumour. Created in <https://BioRender.com>.

High-dimensional analyses including single-cell transcriptomics, T-cell receptor sequencing, spatial transcriptomics, and proteomic profiling are increasingly used to characterise immune evolution during neoadjuvant therapy [15,30]. Such analyses have confirmed expansion of tumour-specific T-cell clones within TDLNs following checkpoint inhibition, supporting the concept that lymphatic structures serve as critical immunologic hubs during treatment response. The availability of paired pre- and post-treatment tumour tissue in the neoadjuvant setting provides a unique opportunity for translational research that is not available in the adjuvant context. Importantly, however, immune-mediated tumour regression frequently produces extensive inflammatory and fibrotic changes within both the primary tumour and regional lymph nodes, potentially complicating radiologic staging and obscuring the distinction between residual tumour and immune-mediated regression, challenges that are central to the remainder of this review.

2.4. Tumour Intrinsic Determinants of Response

While the tumour immune microenvironment and lymphatic immune priming provide the biological basis for sensitivity to checkpoint blockade, tumour intrinsic molecular characteristics also shape the pattern and depth of regression following neoadjuvant immunotherapy. Even within a population of dMMR tumours, responses are not uniform, and understanding the molecular features that distinguish complete from incomplete responses remains an important clinical and biological question.

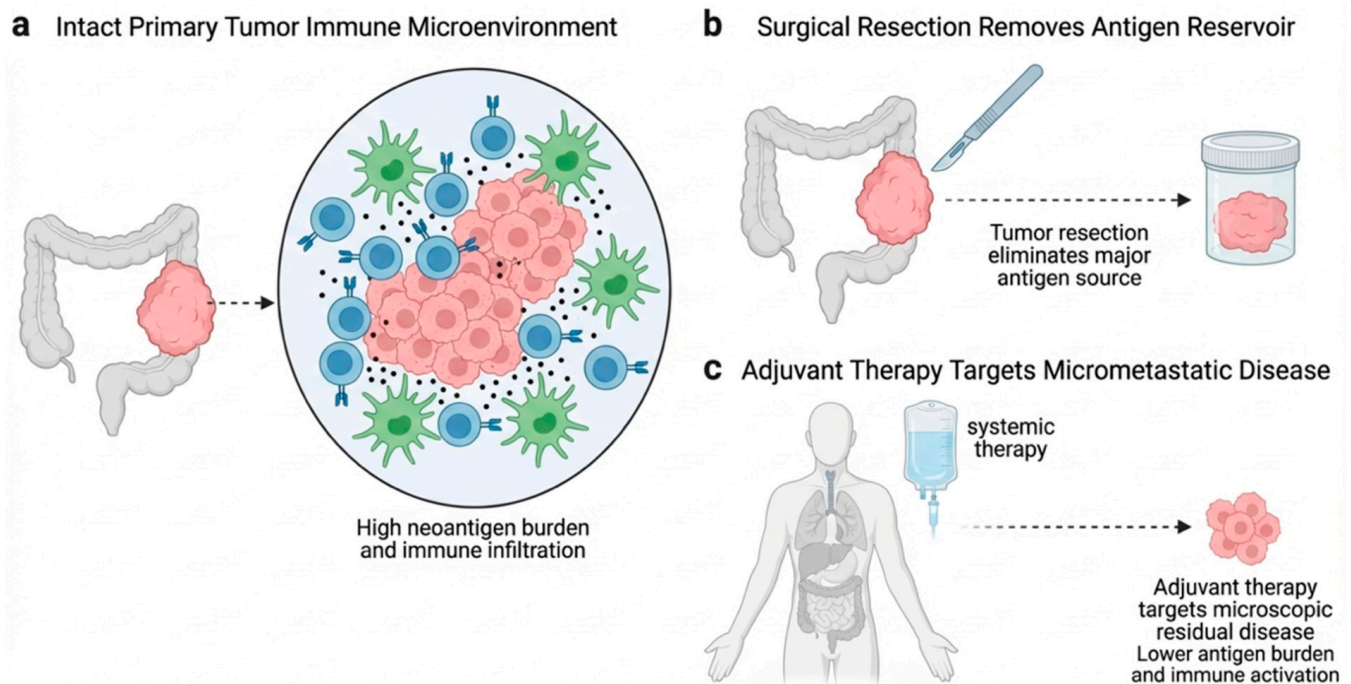


Figure 4. Neoadjuvant immunotherapy paradigm in dMMR colorectal cancer. (a) In localised dMMR colorectal cancer, the intact primary tumour generates a highly immunogenic microenvironment characterised by abundant neoantigen expression and infiltration of immune cells within the tumour and regional lymphatic basin. This setting provides a substantial source of tumour antigens and supports ongoing local immune activation. (b) Surgical resection removes the primary tumour and associated tumour-draining lymphatic tissue, eliminating the major reservoir of tumour antigens and local immune priming. (c) In the adjuvant setting, systemic therapy primarily targets microscopic residual disease. These micrometastatic deposits may have lower antigen burden and reduced immune activation compared with the intact primary tumour, potentially limiting the effectiveness of immune-mediated antitumour responses. Created in <https://BioRender.com>.

Host genetic background is one important determinant. pCR occurred more frequently in Lynch syndrome than in sporadic dMMR tumours in NICHE-2 (79% vs. 61%), and among five Lynch syndrome patients with synchronous second dMMR tumours, four achieved pCR in both lesions [13]. Lynch syndrome patients with advanced malignancy treated with PD-1 inhibitors have demonstrated objective response rates of 70.7% and three-year overall survival of 91.2% [35], and Lynch syndrome has been associated with improved progression-free survival compared with sporadic dMMR in the metastatic setting [36]. Sporadic dMMR colorectal tumours, which most commonly arise through MLH1 promoter hypermethylation and are more frequently BRAF V600E-mutant, may carry a distinct immunobiological profile that tempers response depth despite a shared repair deficiency.

The specific mismatch repair gene altered may also influence the outcome. MSH2/MSH6 co-loss has been associated with longer overall survival than MLH1/PMS2 co-loss, likely reflecting variation in neoantigen quality rather than mutational burden [37,38]. Within Lynch

syndrome, germline PMS2 mutations have been associated with poorer outcomes than other Lynch-associated genes, possibly reflecting PMS2 redundancy and the consequent lower mutational burden in PMS2-deficient tumours [39].

TMB alone has limited predictive value. Baseline TMB was similar in responders and non-responders in NICHE-2, and in NEOPRISM-CRC approximately 40% of TMB-high tumours failed to achieve pCR despite a median TMB of 42 mutations/Mb [13,40]. Insertion–deletion mutational load correlates more closely with response to PD-1 blockade than total TMB [41], and in the NCI-MATCH Z1D study MSI sensor score but not TMB was associated with clinical benefit, suggesting neoantigen quality matters more than quantity.

Other factors further modify outcomes. BRAF V600E has been associated with inferior survival despite checkpoint inhibition, and its co-occurrence with sporadic MLH1 hypermethylation may partly explain poorer outcomes in that group [36,38]. Right-sided tumours fare better than left-sided, and liver or lung metastases are associated with reduced response rates [42,43]. CMS1 tumours demonstrate particularly favourable responses, while non-responders show enrichment of epithelial–mesenchymal transition, angiogenesis, TGF- β , and Wnt/ β -catenin programmes alongside reduced interferon-related transcriptional activity [44,45].

Taken together, these findings confirm that dMMR colorectal cancer is biologically heterogeneous, and that determinants of response extend well beyond dMMR itself. As discussed in the following section, several of these features, particularly stromal activation and immune exclusion programmes, also underpin resistance to checkpoint inhibition in the non-responding minority.

2.5. Resistance to Neoadjuvant Immune Checkpoint Inhibition in dMMR Colorectal Cancer

The transcriptomic correlates of non-response described above point towards overlapping biological mechanisms through which dMMR tumours may evade immune-mediated destruction. Resistance may be primary or acquired, though in the neoadjuvant setting these are difficult to distinguish given that response is typically assessed at a single post-treatment time point. Approximately one-third of patients with metastatic dMMR colorectal cancer will exhibit primary or acquired resistance to checkpoint inhibitors [46,47] (Figure 5), highlighting the need for predictive biomarkers and novel therapeutic strategies [48,49].

The immune architecture of the tumour microenvironment is a central determinant. A constitutive interferon-high immunophenotype enriched in cytotoxic lymphocytes and antigen-presenting macrophages is required for response to checkpoint inhibition, and immune desert tumours predict poor responsiveness even within the dMMR population [50,51]. Stromal TGF- β signalling within cancer-associated fibroblasts restricts CD8⁺ T-cell penetration, and in colorectal cancer metastases TGF- β impairs T-cell recruitment while concurrently instructing SPP1-expressing tumour-associated macrophages to suppress clonal T-cell expansion [52].

Tumour cell-intrinsic evasion mechanisms operate somewhat differently in dMMR colorectal cancer than in other tumour types. JAK1 frameshift mutations similarly occur at high frequency and are associated with reduced interferon response signatures and have been identified as a mechanism of primary resistance to PD-1 blockade in dMMR colon cancer [22,53]. However, patients with JAK1/2 mutations may still derive benefit from anti-PD-1 therapy, and combined PD-1/CTLA-4 blockade may overcome resistance mechanisms that limit monotherapy, with genomic aberrations previously linked to anti-PD-1 resistance present in over half of responding patients in one combination therapy cohort [54,55]. Because nodal clearance depends on the same TDLN antigen presentation and interferon-driven effector function [56] that these alterations disrupt [53,57], JAK1 frameshift and interferon-pathway defects would be expected to compromise regional nodal as well as

primary tumour response [22]; no study has, however, yet directly correlated JAK1 or interferon-signalling status with nodal sterilisation following neoadjuvant immunotherapy in colorectal cancer and any such relationship, though mechanistically plausible, remains unproven [54].

Immunosuppressive cellular programmes add a further layer. Single-cell sequencing in MSI-H metastatic colorectal cancer has implicated IL-1 β -driven myeloid-derived suppressor cells and dysfunctional CD8⁺ T cells as correlates of anti-PD-1 resistance, and an immunosuppressive myeloid ecosystem dominated by SPP1-high macrophages and polymorphonuclear myeloid-derived suppressor cells (PMN MDSCs) represents a major therapeutic hurdle [58,59]. Myeloid Cell Nuclear Differentiation Antigen (MNDNA) promotes further immunosuppression by facilitating PMN-MDSC infiltration through H3K18 lactylation, representing a resistance mechanism specific to MSI-H colorectal cancer [60].

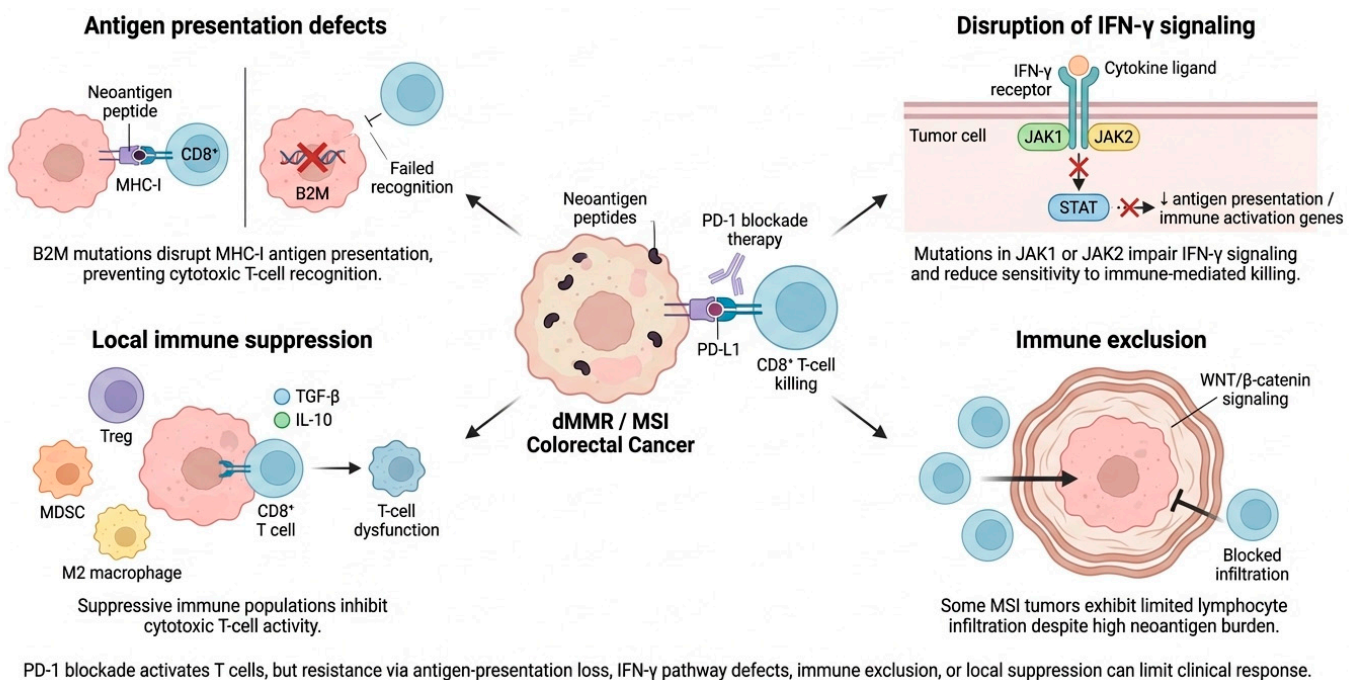


Figure 5. Mechanisms of resistance to immune checkpoint blockade in dMMR colorectal cancer. Mismatch repair-deficient (dMMR) colorectal cancers are typically responsive to PD-1 blockade due to high neoantigen burden and CD8⁺ T-cell infiltration. However, resistance may occur through several mechanisms. Loss of antigen presentation from β 2-microglobulin (B2M) mutations disrupts MHC class I-mediated tumour recognition by cytotoxic T cells. Defects in interferon- γ signalling, including JAK1/JAK2 mutations, impair downstream immune activation. Some tumours exhibit immune exclusion, preventing lymphocyte infiltration despite high mutational burden. Additionally, immunosuppressive tumour microenvironments containing regulatory T cells, myeloid-derived suppressor cells, macrophages, and inhibitory cytokines can promote T-cell dysfunction. These mechanisms collectively contribute to incomplete or transient responses to immune checkpoint inhibition. Created in <https://BioRender.com>.

Co-occurring oncogenic alterations interact with these immune mechanisms beyond their direct effects on response discussed in Section 2.4. Activated WNT/ β -catenin signalling correlates with absent T-cell infiltration, and in a large genomic analysis MSI-high colorectal cancers frequently acquired genetic events permitting immune escape despite high mutational load [61]. Clinically, WNT pathway alterations have been associated with lower objective response rates and shorter survival in MSI patients treated with checkpoint inhibitors [62]. RAS-mutant dMMR tumours exhibit lower neoantigen burden, reduced PD-L1 expression, and fewer infiltrating CD8⁺ T cells than BRAF V600E or RAS

wild-type counterparts, with upregulation of Hedgehog, Wnt, and TGF- β pathways and downregulation of JAK-STAT and T-cell signatures [63].

Intratumour heterogeneity represents a further and underappreciated determinant of resistance. In murine models of dMMR cancer, mismatch repair deficiency alone was insufficient to elicit tumour immunogenicity due to substantial mutational heterogeneity; immunosurveillance shaped clonal architecture but T-cell responses against subclonal neoantigens were blunted, and critically, clonal rather than subclonal neoantigen burden predicted checkpoint inhibitor response in clinical trials of MMR-deficient gastric and colorectal cancer [64]. This finding helps explain why a proportion of TMB-high dMMR tumours fail to respond.

Overcoming resistance will likely require strategies targeting multiple mechanisms simultaneously; however, it occurs less frequently in earlier stage disease. PD-1 blockade combined with TGF- β inhibition restores T-cell infiltration and improves antitumour immunity in preclinical models [65,66], and additional approaches under investigation include myeloid reprogramming through PI3K γ , CSF1R, and TREM2 targeting, WNT/ β -catenin inhibition, and microbiome-targeted interventions [48,59]. Neoantigen-targeted vaccines and Werner helicase inhibition represent emerging strategies specific to MMR-deficient tumours [67].

3. Limitations of Clinical Nodal Staging

Conventional imaging modalities and reporting systems were developed in the context of cytotoxic therapies and rely primarily on structural criteria, nodal size and morphology, that perform only moderately in distinguishing reactive lymphadenopathy from metastatic disease. These limitations are particularly pronounced in immunogenic tumour types such as dMMR colorectal cancer.

In colon cancer, contrast-enhanced CT is the standard modality for preoperative staging. Meta-analytic data demonstrate pooled sensitivity of 71% (95% CI 59–81%) and specificity of 67% (95% CI 46–83%) for detection of pathological node-positive disease [68], findings consistent with large population-based studies showing only moderate agreement between clinical and pathological N stage [69,70]. These limitations are especially relevant in dMMR tumours. Compared with mismatch repair-proficient cancers, dMMR colon cancers appear to have a lower frequency of lymph node metastasis despite adverse histologic features, with lower lymph node ratios and reduced odds of nodal metastasis suggesting that host immune responses may suppress nodal dissemination [71,72]. At the same time, they are often associated with increased lymph node yield at surgery, thought to reflect greater immune activation rather than differences in surgical technique [73,74]. Reactive lymphadenopathy driven by immune infiltration may therefore produce enlarged regional nodes that mimic metastatic disease on size-threshold-based CT staging [75,76]. Lower concordance between radiologic and pathological nodal staging in dMMR compared with mismatch repair-proficient tumours was demonstrated in the FOxTROT trial [77]. A subset of CT features, including tumour length and largest lymph node diameter, show greater reproducibility and may warrant further validation as staging markers [69,78].

These limitations raise an important therapeutic question in dMMR colon cancer. Because baseline staging is unreliable and these tumours demonstrate exceptional sensitivity to checkpoint inhibition, broader neoadjuvant immunotherapy carries the risk of overtreatment, particularly given the favourable prognosis following surgery alone in stage II and low-risk stage III disease. The development of organ-preserving strategies may partly resolve this concern, particularly in patients with Lynch syndrome, in whom repeated resections for metachronous tumours are common and immunotherapy does not prevent the development of new primary malignancies [79,80].

In rectal cancer, pelvic MRI provides improved soft tissue resolution and is central to locoregional staging, allowing evaluation of tumour depth, mesorectal fascia involvement, and regional nodal compartments. However, nodal staging remains imperfect: meta-analyses report pooled sensitivities and specificities of approximately 73–74% for detecting nodal metastases [81], and neither nodal size nor morphology reliably distinguishes benign from malignant nodes. Current MRI criteria incorporate a combination of size and morphologic features—including round shape, irregular borders, heterogeneous signal intensity, and internal nodal heterogeneity—but these features lack sufficient accuracy for dependable staging, with small nodes able to harbour metastatic deposits while benign inflammatory nodes may demonstrate suspicious characteristics [82,83]. Population-based data from the Netherlands demonstrate that dMMR rectal cancers are significantly more likely than mismatch repair-proficient tumours to be clinically overstaged with respect to nodal status: nodal overstaging occurred in approximately one-third of dMMR tumours, whereas understaging was relatively uncommon [84]. Despite presenting with more advanced clinical stage, patients with dMMR rectal cancer demonstrate improved survival outcomes compared with mismatch repair-proficient tumours, a paradox consistent with systematic overstaging at baseline [85]. Emerging imaging observations also suggest that certain nodal features, such as lymph node necrosis, may be associated with MSI biology itself rather than metastatic burden, further complicating radiologic interpretation [86]. Immune activation within TDLNs, producing reactive enlargement, lymphoid hyperplasia, and inflammatory remodelling, is likely central to this systematic overstaging.

In general, dMMR colorectal cancer carries a favourable prognosis in early-stage disease, with high cure rates following complete resection of stage I and many stage II tumours. This advantage diminishes with nodal involvement, and dMMR tumours are additionally associated with higher T stage at presentation and increased risk of metachronous peritoneal metastases [87,88]. Current NCCN guidelines accordingly recommend neoadjuvant checkpoint inhibition for locally advanced dMMR/MSI-H colon cancer, including cT4b or bulky nodal disease [89]. In the adjuvant setting, the relative chemoresistance of dMMR tumours has prompted incorporation of immunotherapy into postoperative strategies, with the ATOMIC trial establishing oxaliplatin-based chemoimmunotherapy as a preferred approach, though this commits patients to 6 months of chemotherapy and a year of immunotherapy, in contrast to the shorter neoadjuvant courses demonstrating comparable or superior efficacy in several recent trials [11,13,90].

These therapeutic considerations are compounded by fundamental limitations of conventional imaging in dMMR tumours. The immunologic activity of dMMR cancers shapes the lymph node microenvironment in ways that size-based staging criteria cannot capture; even at baseline, immune activation within TDLNs may precede overt metastatic involvement, producing a biological continuum from purely reactive enlargement to early nodal disease that imaging cannot reliably distinguish. Following treatment, immune-mediated regression may leave persistent structural abnormalities despite eradication of viable tumour, causing conventional imaging to systematically underestimate response. Together, these features highlight the need for imaging approaches that reflect immune-mediated nodal biology rather than structural change alone, a challenge explored in detail in the sections below.

4. Clinical Evidence for Neoadjuvant Immune Checkpoint Inhibition

4.1. Metastatic Disease: Establishing dMMR as a Predictive Biomarker

The rationale for neoadjuvant immunotherapy in dMMR colorectal cancer emerged directly from the marked sensitivity of these tumours to checkpoint inhibition in metastatic disease. The first signal was observed during early phase I PD-1 inhibitor trials, in which a

single patient with colorectal cancer achieved a durable complete response; retrospective analysis revealed the tumour to be dMMR [5]. Subsequent randomised trials confirmed this biology. The phase III KEYNOTE-177 trial demonstrated that pembrolizumab significantly improved progression-free survival compared with chemotherapy as first-line treatment in metastatic MSI-H/dMMR colorectal cancer [1]. Combination checkpoint blockade further extended outcomes: in CheckMate-142, nivolumab plus ipilimumab produced durable responses in previously treated disease [10,91], and the phase III CheckMate-8HW trial demonstrated superior progression-free survival with dual checkpoint inhibition in the first-line metastatic setting [46,47]. These findings established immune checkpoint inhibition as the standard first-line systemic therapy for metastatic dMMR colorectal cancer. The progressive improvement in response rates with earlier-line use and the superior efficacy of dual over single-agent checkpoint blockade provided a compelling rationale for moving immunotherapy into the neoadjuvant setting, where the relative immune permissiveness of localised dMMR disease has since been demonstrated by unprecedented pathological response rates.

4.2. Neoadjuvant Immunotherapy in Localised Disease

The most dramatic responses to neoadjuvant checkpoint inhibition have been observed in localised dMMR colorectal cancer. In rectal cancer, the phase II dostarlimab trial demonstrated clinical complete response (cCR) in all patients who completed treatment, allowing avoidance of chemoradiation and surgery in the initial cohort [92]. Subsequent expansion to 117 patients across two cohorts confirmed sustained cCR in the majority, with two-year recurrence-free survival of 92%, and curative surgery remained feasible for patients requiring salvage resection [93]. Similar outcomes have been reported with other PD-1 inhibitors, with cCR rates frequently exceeding 70–80% [94–96].

Parallel findings have been reported in colon cancer. In the NICHE trial, a short course of nivolumab plus ipilimumab before surgery produced pathological response in all dMMR tumours and pCR in 69% [11]. The subsequent NICHE-2 trial, enrolling 111 patients with locally advanced dMMR colon cancer, confirmed major pathological response in 95% of patients and pCR in 68% [12,13]. The NICHE-3 trial subsequently explored nivolumab plus relatlimab (LAG-3 blockade) in the same setting, achieving pCR in 68% of patients, suggesting that alternative checkpoint combinations may produce comparable response rates [97]. Additional studies report similarly high response rates with alternative checkpoint inhibitors: in the PICC trial, neoadjuvant toripalimab achieved pCR rates of 65–88% [98], and in the NEOCAP trial, camrelizumab plus apatinib produced combined clinical and pCR in approximately 73% of patients [99].

More recently, early-phase data for novel combinations including botensilimab plus balstilimab (NEST-1) and the PD-1 inhibitor tislelizumab (BGB-A317-214) have reported pCR rates of 67% and 62% respectively [100,101], while ultrashort dosing strategies, including single-dose pembrolizumab in RESET-C (pCR 44%) and one to two doses in IMHOTEP (pCR 39%), suggest that meaningful pathological responses may be achievable with minimal treatment exposure, collectively reinforcing the breadth of agents and schedules capable of producing deep responses in this tumour type [100–103]. Key prospective trials of neoadjuvant immune checkpoint inhibition in dMMR/MSI-H colorectal cancer, including available data on nodal sterilisation and non-operative management outcomes, are summarised in Table 1.

Table 1. Key prospective trials of neoadjuvant immune checkpoint inhibition in dMMR/MSI-H colorectal cancer.

Country	Trial Name	Phase	n	Study Population	Neoadjuvant Therapy	Treatment Duration	pCR	Nodal Sterilisation (ypN0)	NOM (n, %)	Grade 3+ AEs	References
Netherlands	NICHE-1	2	32	Stage I–III dMMR colon	Nivolumab + ipilimumab	2 doses/4 weeks	69%	NR	0	12%	Chalabi et al., 2020 [11]
China	PICC	2	34	Stage II–III dMMR/MSI-H CRC	Toripalimab ± celecoxib	6 cycles/3 months	65% vs. 88%	97% (33/34)	0	0%	Hu et al., 2022 [98]; Shen et al., 2025 [104]
Japan	VOLTAGE-A	Ib/II	5 MSI-H	Stage II–III dMMR rectal	CRT → nivolumab × 5	5 cycles Q2W	60%	NR	0	8%	Bando et al., 2022 [95]; Tsukada et al., 2024 [96]
USA	–	2	12	Stage II–III dMMR rectal	Dostarlimab Q3W × 9	6 months	cCR 100%	N/A (NOM)	12 (100%)	0%	Cercek et al., 2022 [92]
China	–	2	17	Stage II–III dMMR rectal	Sintilimab Q3W × 4–8	4–8 cycles	50%	NR	9 (53%)	6%	Chen et al., 2023 [94]
USA	–	2	35	Localised MSI-H solid tumours	Pembrolizumab Q3W × 8	6 months	65% (79% CRC)	NR	18 (51%)	9%	Ludford et al., 2023 [105]; LaPelusa et al., 2025 [106]
Netherlands	NICHE-2	2	111	Stage III dMMR colon	Nivolumab + ipilimumab	2 doses/4 weeks	68%	87% (97/111)	0	4%	Chalabi et al., 2024 [13]
UK	NEOPRISM-CRC	2	32	High-risk stage II–III dMMR/MSI-H CRC	Pembrolizumab Q3W × 3 (TMB-high/medium) or × 1 (TMB-low)	3 cycles/9 weeks	59% (evaluable); 55% ITT	NR	0	0%	Shiu et al., 2024 [40]
China	NEOCAP	2	52	Stage II–III dMMR/MSI-H CRC	Camrelizumab + apatinib	8 cycles/6 months	61%	NR	24 (46%)	38%	Yu et al., 2024 [99]
USA	NEST-1	2	3 MSI-H	Stage I–III dMMR CRC	Botensilimab + balstilimab	3 weeks	67% (2/3)	NR	0	0%	Kasi et al., 2024 [100] *
Netherlands	NICHE-3	2	59	Stage I–III dMMR colon	Nivolumab + relatlimab	2 doses/2 weeks	68%	NR	Optional	5%	de Gooyer et al., 2024 [97]
France	IMHOTEP	2	70 (interim)	Localised dMMR/MSI tumours	Pembrolizumab Q6W × 1–2	1–2 doses	39% (CRC 41%)	NR	7 (cCR, declined surgery)	6%	Coutzac et al., 2022 [103]
Denmark	RESET-C	2	85	Stage I–III dMMR colon	Pembrolizumab × 1 dose	Single cycle/3–5 weeks	44% (61% stage I–II; 33% stage III)	NR	1 (1%)	8%	Qvortrup et al., 2025 [102]
USA	–	2	117	Stage I–III dMMR solid tumours	Dostarlimab Q3W × 9	6 months	cCR 82%; 100% rectal	N/A (NOM)	82 (80%)	5%	Cercek et al., 2025 [93]
China	–	Ib	101	Stage II–III dMMR colon	IBI310 + sintilimab vs. sintilimab	2 doses/6 weeks	78% vs. 47%	NR	0	6% vs. 4%	Wang et al., 2025 [107]
China	WINDOW	2	24	Stage II–III dMMR CRC	Tislelizumab Q3W (ctDNA-guided)	ctDNA-guided	92% CR	N/A (NOM)	20 (83%)	NR	Zhang et al., 2025 [108]
China	BGB-A317-214	2	33	Stage II–III dMMR CRC	Tislelizumab Q3W × 3	3 cycles/9 weeks	62%	NR	3 (9%)	3%	Chen et al., 2026 [101]

Abbreviations: cCR, clinical complete response; CRC, colorectal cancer; CRT, chemoradiotherapy; ctDNA, circulating tumour DNA; dMMR, deficient mismatch repair; ITT, intention-to-treat; MSI-H, microsatellite instability-high; NOM, non-operative management; NR, not reported; pCR, pathological complete response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; TMB, tumour mutational burden; ypN0, pathologically node-negative at resection. * Conference abstract; data not yet peer-reviewed. N/A = Not Applicable.

4.3. Nodal Pathological Response and Concordance with Primary Tumour

Impressive rates of nodal sterilisation is a consistent finding across neoadjuvant immunotherapy trials in dMMR colorectal cancer: in NICHE-2, only 14 of 111 patients (13%) had tumour-positive lymph nodes at resection. However, primary tumour and nodal responses are not always concordant; pathological waterfall plots demonstrate that complete regression of the primary tumour can coexist with residual nodal disease, and a single residual tumour cell within a lymph node has been reported despite primary tumour pCR in real-world experience [13,109]. These observations have direct implications for organ preservation strategies: the absence of viable primary tumour on endoscopy and MRI cannot be assumed to confirm regional nodal sterilisation, and current response assessment frameworks, designed primarily to evaluate the primary tumour bed, cannot reliably interrogate the nodal compartment without surgical resection.

The biological basis of this discordance, and its implications for pathological interpretation, are explored in Section 6. In the context of organ preservation strategies, particularly for rectal cancer, immune mediated changes can challenge response assessment [110,111]. Addressing this gap will be essential for the safe expansion of non-operative management strategies, particularly in patients with high nodal burden at baseline.

5. Radiologic and Endoscopic Assessment of Response

5.1. CT-Based Response Assessment in Colon Cancer

CT reflects structural change rather than tumour viability, and the imaging frameworks developed for chemotherapy or chemoradiation provide an imperfect basis for response assessment after immunotherapy. Evidence from neoadjuvant ICI studies consistently demonstrates substantial discordance between radiographic findings and pathological response. In NICHE-2, although pCR occurred in 68% of patients, radiographic complete response was documented in only two of the seventy-five patients with pCR and available imaging; thus, more than 97% of patients with pCR failed to satisfy conventional radiographic response criteria [13]. In a retrospective series evaluating radiologic–pathologic correlation after anti-PD-1 therapy, 92.9% of patients with pCR continued to demonstrate apparent residual disease on CT [112].

A post hoc radiologic analysis of the PICC phase II trial found that among 36 patients with pCR after neoadjuvant PD-1 blockade, conventional CT size-based metrics such as tumour diameter or percentage change from baseline did not reliably distinguish tumours with pCR from those with residual disease [113]. However, qualitative imaging features reflecting tissue remodelling appeared more informative: tumours with pCR demonstrated smaller post-treatment wall thickness, greater reductions in tumour thickness, and absence of vascular, nodular, and extramural enhancement signs. Radiologic–pathologic discordance has also been reported in metastatic disease: four of five patients who underwent metastasectomy after radiologic partial response to pembrolizumab for dMMR metastatic colorectal cancer had pCR on pathological examination [114]. In a pooled analysis of 396 patients with dMMR/MSI-H colorectal cancer treated with neoadjuvant immunotherapy, overall discordance between radiologic and pathological response was 59.6%, with significantly higher discordance in colon cancer than in rectal cancer (64.2% vs. 34.9%); among 238 patients with confirmed pCR, radiologic assessment incorrectly suggested residual disease in a substantial proportion (OR 61.41; 95% CI 10.05–375.27; $p < 0.00001$) [115]. Taken together, these data indicate that persistent nodal enlargement or mural abnormalities on CT after immunotherapy more often reflects immune-mediated remodelling rather than viable residual malignancy.

5.2. MRI and Endoscopic Restaging in Rectal Cancer

In rectal cancer, pelvic MRI is the dominant modality for post-treatment restaging because of its superior soft tissue contrast and its ability to evaluate both the primary tumour and mesorectal nodal compartments and comparative data suggest MRI outperforms FDG-PET for complete response identification in this setting [116]. MRI response assessment after neoadjuvant therapy typically incorporates tumour morphology on T2-weighted imaging, MRI tumour regression grade, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) changes, and regression of suspicious lymph nodes within the mesorectal and extramesorectal compartments [82].

Several MRI-derived parameters may improve nodal prediction. Reduction in lymph node size appears particularly informative: a 70% reduction in the diameter of the largest node predicted ypN0 status with an area under the curve of 0.818, sensitivity of 93.3%, and negative predictive value exceeding 95% [117]. Node disappearance on restaging MRI performed similarly, while a short-axis cutoff of 2.2 mm achieved an area under the curve of 0.83, sensitivity of 79.5%, and negative predictive value of 91.1%. Morphological criteria may further refine prediction: a multicentre three-feature method incorporating signal homogeneity, interruption of vessels, and tail sign achieved an AUC of 0.83 and outperformed conventional ESGAR criteria [118]. DWI provides additional nodal information: absence of nodal signal on high-b-value DWI has been associated with sensitivity and negative predictive value approaching 100% for ypN0 status, though specificity remained low [82]. After immunotherapy-based neoadjuvant treatment, a 3 mm short-axis cutoff may be particularly relevant, identifying ypN0 status with an AUC of 0.76, consistent with the possibility that immune-mediated nodal regression leaves smaller residual nodal structures than those observed after conventional chemoradiation [119].

However, the immunotherapy setting introduces additional complexity. In studies of neoadjuvant ICI for dMMR rectal cancer, conventional MRI and endoscopy both demonstrated limited ability to identify pCR, with AUC values of approximately 0.54–0.57 [119]. DWI improves functional assessment but does not fully resolve the problem. Post-treatment ADC values are consistently higher in tumours achieving pCR than in non-responders [120,121], and meta-analytic data demonstrate that percentage increases in ADC predicted pCR with an AUC of 0.856, sensitivity of 80%, and specificity of 76% [122]. Combined DWI and T2-weighted approaches using DWI-modified MR tumour regression grade have achieved AUC values of 0.90 for predicting pCR in neoadjuvant settings, with specificity of 89% and negative predictive value of 93% [123]. However, these approaches require specific validation in immunotherapy-treated dMMR rectal cancer, where immune-mediated regression produces distinct tissue changes.

Dedicated descriptions of post-immunotherapy MRI regression patterns further illustrate these challenges. In a retrospective analysis of 14 MSI-H/dMMR rectal cancers treated with neoadjuvant PD-1 blockade, all patients achieved pCR, yet MRI appearances were heterogeneous, including split scar sign, fibrotic response, lesion disappearance, and persistent intermediate T2 signal [124]. Mucinous tumours frequently retained T2-hyperintense residues despite complete pathological response, a pattern that may lead to false-positive residual disease assessment and underscores the inadequacy of imaging criteria developed for cytotoxic therapy.

Endoscopic assessment therefore plays a critical complementary role. Endoscopy directly evaluates mucosal regression and may detect treatment response earlier than cross-sectional imaging. In a retrospective MD Anderson cohort of localised MSI-H/dMMR colorectal cancer treated with anti-PD-1 therapy, endoscopic complete response occurred in approximately 45% of patients after six to eight treatment cycles, whereas imaging complete response occurred in only 19% [125]. Similar findings were observed in the

NEOCAP trial, where 54% of patients achieved cCR after six months of camrelizumab plus apatinib [99]. NCCN guidelines accordingly recommend multimodal assessment combining MRI, endoscopy, digital rectal examination, and biopsy when determining cCR and eligibility for non-operative management [126]. Prospective data from the OPRA trial confirm that flexible sigmoidoscopy and MRI restaging achieve high sensitivity for identifying true complete response after total neoadjuvant therapy, with endoscopic criteria independently predictive of sustained organ preservation [127,128].

5.3. Immune-Related Regression Patterns and Pseudoproggression

Immune checkpoint blockade produces atypical response patterns not captured by conventional RECIST criteria. Pseudoproggression, in which lesions enlarge or remain conspicuous because of immune cell infiltration and inflammatory remodelling rather than true tumour progression, occurs in approximately 10% of patients with metastatic MSI-H/dMMR colorectal cancer and typically arises within the first three months of treatment [129]. In the neoadjuvant rectal cancer setting, pseudoproggression and pseudoresidue appear particularly common: Xie and colleagues reported pseudoproggression in 23.1% and pseudoresidue in 76.9% of patients after neoadjuvant ICI, corresponding pathologically to fibrogenesis and dense lymphocytic infiltration rather than viable tumour [130].

A related phenomenon is nodal immune flare, in which lymph nodes enlarge after immunotherapy because of immune activation rather than metastatic progression. In resectable non-small-cell lung cancer, nodal immune flare occurred in 16% of patients treated with neoadjuvant checkpoint blockade but in none treated with chemotherapy [131]. Sarcoid-like granulomatous lymphadenopathy after checkpoint inhibition may similarly mimic nodal metastases on CT or PET imaging [132]. These findings collectively indicate that structural imaging alone is insufficient to determine nodal response after neoadjuvant ICI, and that persistent radiologic abnormalities, including nodal enlargement, may reflect immune-mediated regression rather than viable residual malignancy. The performance characteristics, key limitations in the dMMR context, and current clinical role of each imaging modality are summarised in Table 2.

Table 2. Imaging modalities for nodal staging and response assessment in dMMR colorectal cancer.

Modality	Sensitivity for Nodal Staging	Specificity for Nodal Staging	Performance Post-Immunotherapy	Key Limitations in dMMR Context	Current Clinical Role	References
CT (colon)	62–64%	67–70%	Poor; only 2/75 (3%) pCR cases showed radiographic CR in NICHE-2	Immune-mediated lymphadenopathy mimics metastases; size-based criteria unreliable in immunogenic tumours	Standard pre- and post-treatment staging for colon cancer	Shkurti et al., 2023 [70]; Shkurti et al., 2026 [69]; Chalabi et al., 2024 [13]
Pelvic MRI (rectal)	60–77%	65–77%	Limited; AUC 0.54–0.57 for pCR identification after immunotherapy-based neoadjuvant therapy; persistent MRI abnormalities frequent despite pCR	Reactive lymphoid hyperplasia and inflammatory remodelling persist after immune regression; mucinous tumours retain T2 signal despite pCR	Standard staging and response assessment in rectal cancer; combined with DWI/ADC	Korngold et al., 2025 [82]; Miao et al., 2025 [119]; Vanderbecq et al., 2026 [124]
FDG-PET	43% (nodal)	80% (nodal)	Early metabolic responses detectable; SUV falls to background in some responders	Immune cell infiltration increases FDG uptake, mimicking progression (pseudoproggression); low sensitivity for nodal metastases	Investigational for response assessment; limited data in dMMR CRC	Cercek et al., 2022 [92]; Kariv et al., 2025 [116]

Table 2. Cont.

Modality	Sensitivity for Nodal Staging	Specificity for Nodal Staging	Performance Post-Immunotherapy	Key Limitations in dMMR Context	Current Clinical Role	References
ImmunoPET (e.g., 89Zr-CD8, 68Ga-grazytracer)	Not established	Not established	CD8-PET uptake correlates with response; 68Ga-grazytracer PET showed superior predictive value vs. RECIST for PFS	Not yet validated in dMMR colorectal cancer; phase 1–2 data only; significant inter-lesion heterogeneity	Investigational; potential to image immune activation in primary and nodal compartments	Kist de Ruijter et al., 2022 [133]; Farwell et al., 2022 [134]; Shen et al., 2024 [123]
USPIO-enhanced MRI	88–90% (pooled)	93–96% (pooled)	Not evaluated specifically post-immunotherapy	Reactive/inflammatory nodes may show false-positive signal; limited availability; reduced accuracy for small nodes in rectal cancer	Not in routine use; available in specialist centres	Will et al., 2006 [135]; Wu et al., 2011 [136]; Stijns et al., 2021 [137]
Sigmoidoscopy	N/A (mucosal only)	N/A	AUC 0.80–0.84 for cCR after CRT; 96% sensitivity for true response in OPRA trial; poor performance (AUC 0.54–0.57) after immunotherapy-based neoadjuvant therapy	Cannot assess nodal compartment; limited to rectal cancer surveillance	Recommended by NCCN as part of multimodal response assessment in rectal cancer	van der Sande et al., 2021 [127]; Williams et al., 2025 [128]; Miao et al., 2025 [119]
Radiomics	N/A	N/A	AUC 0.90 for pCR prediction in dMMR/MSI-H CRC after neoadjuvant anti-PD-1 therapy (immunophenotype-guided model); AUC 0.79–0.98 for pCR in CRT setting	Requires standardisation; limited validation in dMMR CRC post-immunotherapy; heterogeneity across studies	Investigational; promising for integration with genomic/immunologic biomarkers	Zhang et al., 2023 [138]; Shayesteh et al., 2021 [139]; Qin et al., 2024 [140]; Liu et al., 2017 [141]

Abbreviations: AUC, area under the receiver operating characteristic curve; cCR, clinical complete response; CRT, chemoradiotherapy; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; FDG, fluorodeoxyglucose; pCR, pathological complete response; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SUV, standardised uptake value; USPIO, ultra-small superparamagnetic iron oxide; dMMR, deficient mismatch repair. N/A = Not Applicable.

5.4. Avoiding Overtreatment from Immune-Related Nodal Change

Because pseudoprogression, pseudoresidue, and nodal immune flare can each mimic residual or progressive nodal disease [115,130,131], several practical principles help guard against unnecessary surgery or overtreatment. Isolated nodal enlargement or persistent metabolic activity on FDG-PET should not, in itself, be interpreted as treatment failure, particularly within the first three months of therapy, when immune-related flare is most frequent [129,142]. Apparent progression or a persistent nodal abnormality is better adjudicated by multimodal and longitudinal assessment than by any single cross-sectional study [143]: in rectal cancer this combines MRI morphology with DWI and ADC change [122], endoscopic mucosal assessment, and the trajectory of ctDNA [106], whereas in colon cancer, where the surveillance toolkit is more limited, greater weight necessarily falls on interval CT and ctDNA dynamics [144]. A short confirmatory interval with repeat imaging, rather than immediate salvage resection, is appropriate where the suspicion of viable disease is equivocal [142], and image-guided or endoscopic biopsy of a persistently abnormal node should be obtained where it is feasible and would alter management [131]. Decisions to proceed to surgery, to intensify therapy, or to continue surveillance are best made within an experienced multidisciplinary team [126], since the imaging and pathological features of immune-mediated regression remain unfamiliar in routine practice and the consequences of misclassification, i.e., an unnecessary proctectomy or colectomy in a patient who has achieved genuine tumour eradication, are substantial [112,115,130].

6. Pathologic Features of Nodal Response

6.1. Patterns of Regression and Frequency of Nodal Sterilisation

Pathological examination provides the most direct evidence of nodal response and can distinguish viable metastatic deposits from treatment-induced immune remodelling, a distinction that imaging cannot reliably make. For context, ypN0 status is achieved in approximately 69–80% of patients following conventional cytotoxic therapy for rectal cancer [107,145]. In the PROSPECT trial, ypN0 rates were 75% with neoadjuvant FOLFOX and 77% with chemoradiotherapy [145]. Intensification of neoadjuvant therapy further increases response rates and nodal clearance, with the addition of systemic chemotherapy to chemoradiotherapy increasing ypN0 rates compared with chemoradiotherapy alone (75% vs. 62%, $p = 0.030$) [146,147]. Approximately 20% of ypN0 patients demonstrate histologic features of complete nodal regression including fibrosis, histiocytosis, or mucin pools, and these patients have improved disease-free survival compared with ypN0 patients without such regression changes [148].

Nodal sterilisation rates are substantially higher after neoadjuvant immunotherapy in dMMR colorectal cancer. In NICHE-2, only 14 of 111 patients (13%) had tumour-positive lymph nodes at resection, indicating nodal sterilisation in 87% of cases [13]. Importantly, pathological waterfall plots demonstrate that in some cases where the primary tumour had completely regressed, residual disease persisted only within lymph nodes, underscoring that regression of primary tumours and nodal metastases may occur asynchronously following checkpoint blockade [13]. Several mechanisms may account for this discordance, in which the primary tumour achieves pCR while viable disease persists within regional nodes. The nodal and primary compartments differ in immune microenvironment and antigen-presentation context [30,149], such that effector T-cell access, local drug exposure, and the kinetics of immune-mediated regression need not be synchronous between the two sites [150]. Nodal deposits may also be enriched for subclonal populations bearing fewer immunogenic neoantigens because clonal rather than subclonal neoantigen burden predicts checkpoint inhibitor response [151]. This phenomenon is not unique to colorectal cancer: discordant primary tumour and nodal pathological responses have been reported after neoadjuvant immunotherapy in non-small-cell lung cancer [150,152], head and neck cancer [153,154], and melanoma [155,156], and spatial profiling studies confirm that TDLNs respond differently to checkpoint inhibition than paired primary tumours across radiological, metabolic, and pathological measures [157]. Real-world experience in MSI-H gastrointestinal cancers further illustrates this point, with residual tumour cells identified within lymph nodes despite primary tumour pCR [109]. Checkpoint blockade also induces immune-mediated changes within TDLNs: expansion of tumour-specific CD8⁺ effector-memory T cells has been demonstrated following checkpoint inhibition and may contribute to subsequent tumour infiltration by cytotoxic T cells [30], reinforcing the concept that lymph nodes function as active immunologic compartments, not merely as potential sites of metastatic spread.

6.2. Histologic Characteristics

Histologically, regressed lymph nodes after checkpoint blockade display features of immune activation and remodelling rather than simple scar formation. These include lymphoid hyperplasia, prominent germinal centre activity, stromal fibrosis, and dense infiltration by lymphocytes and plasma cells [13,130]. Single-cell RNA sequencing and T-cell receptor profiling of TDLNs have demonstrated expansion of tumour-specific CD8⁺ effector-memory T cells and CD4⁺ follicular helper T cells following ICI, the latter potentially enhancing local humoral immune responses and antigen presentation [30]. Non-caseating granulomatous inflammation represents another pattern of immune-mediated

nodal remodelling; in the NEOSTAR trial, nodal immune flare was characterised by non-caseating granulomas and inflammatory infiltrates in enlarged lymph nodes without viable tumour [131]. Similar granulomatous reactions have been reported in melanoma, where enlarged lymph nodes contained numerous non-necrotising granulomas without tumour evidence [132].

Acellular mucin pools may persist in both the primary tumour and regional lymph nodes after neoadjuvant immunotherapy. In the extended dostarlimab cohort, mucinous residues were observed in some rectal cancer patients managed successfully with non-operative surveillance, suggesting that persistent mucin may represent immune-mediated tumour regression rather than viable malignancy [92,93]. NCCN guidance similarly states that acellular mucin pools following neoadjuvant therapy should not be interpreted as residual malignancy [126]. When present in both primary tumour and lymph node compartments, acellular mucin pools have been associated with more aggressive biology in conventional neoadjuvant therapy cohorts [158], though the significance of nodal mucin deposition after ICI warrants further investigation.

6.3. Lymph Node Regression Grading and Challenges in Pathological Interpretation

Despite the importance of pathological assessment, no standardised regression grading system exists specifically for lymph nodes after immune checkpoint inhibition. Existing systems, including the Mandard, Dworak/Rödel, and AJCC/CAP systems for primary tumours [159,160], were developed for cytotoxic therapy and do not capture immune-mediated patterns of nodal remodelling. Lymph node-specific regression grading explored in chemoradiotherapy cohorts, including grading according to the proportion of fibrosis and residual tumour, and metrics such as LRG-max, LRG-sum, and LRG-ratio [161,162], also lack validation in the immunotherapy setting.

Several additional challenges complicate pathological interpretation after ICI. First, distinguishing minimal residual disease from extensive fibrosis or inflammatory infiltrates can be difficult when only small clusters of tumour cells remain. Isolated tumour cells measuring less than 0.2 mm are classified as pN0 according to NCCN and AJCC guidelines, whereas micrometastases of 0.2–2 mm are classified as pN1, but the clinical significance of these minimal deposits after immunotherapy remains uncertain. Second, lymph node yield may be reduced following neoadjuvant therapy because of treatment-induced nodal involution; current guidelines recommend evaluation of at least 12 lymph nodes for accurate staging, a threshold that may not always be achievable [89,126]. Third, trials reporting of nodal response remains inconsistent: some studies report ypN stage alone, while few integrate baseline nodal staging, post-treatment imaging, and pathological findings within a unified framework. Development of an immunotherapy-specific nodal regression grading system and standardised reporting framework represents an important unmet need.

These pathological observations have important implications for clinical management. The high frequency of nodal sterilisation after neoadjuvant immune checkpoint inhibition, together with the frequent discordance between imaging and true tumour viability, challenges traditional assumptions regarding nodal disease in colorectal cancer. In conventional management, the presence of nodal metastases drives adjuvant chemotherapy recommendations and influences the extent of surgical resection. If nodal metastases can be reliably eradicated by immunotherapy, and if imaging cannot reliably distinguish residual disease from immune-mediated regression, then both the indication for adjuvant therapy and the required extent of lymphadenectomy or even the necessity for resection may warrant reconsideration in selected patients achieving deep pathological responses. Realising this potential, however, will require the development of validated tools capable of confirming nodal sterilisation without reliance on histological examination of a surgical specimen.

7. Implications for Surgical Management

7.1. Organ Preservation in Rectal Cancer

The most immediate surgical implication of neoadjuvant immunotherapy has been the emergence of organ preservation strategies. Non-operative management (“watch-and-wait”) was originally developed for patients achieving cCR after chemoradiation [163,164] and response rates improved further with total neoadjuvant therapy in the OPRA trial [165,166]. Response rates with immune checkpoint inhibition in dMMR rectal cancer appear substantially higher than with conventional therapy. In the prospective dostarlimab trial, all patients who completed treatment achieved cCR, enabling avoidance of chemoradiation and surgery [92]; updated analyses of 117 patients across two cohorts confirmed sustained responses with two-year recurrence-free survival of 92%. This rose to 96% when restricted to rectal cancer only. Importantly, curative surgery remained feasible for patients requiring salvage resection [93]. A systematic review of 19 studies including 504 patients with dMMR/MSI-H rectal cancer treated with neoadjuvant ICIs reported cCR rates ranging from 75% to 100%, with organ preservation achieved in up to 100% of patients [167]. Additional cohort studies have demonstrated durable disease control with long-term disease-free survival approaching 100% in some series [168–173]. Reflecting these data, NCCN guidelines now recognise non-operative management as an option for dMMR rectal cancer patients achieving cCR following neoadjuvant ICI, provided that surveillance is performed within experienced multidisciplinary centres [126].

It must be emphasised that, in contrast to rectal cancer, non-operative management of colon cancer is not established practice and at present remains investigational. The implications for colon cancer are emerging but remain less clear, constrained by the limitations of CT and colonoscopy relative to the MRI–sigmoidoscopy combination available in rectal cancer. Colonoscopic evaluation is less well tolerated than sigmoidoscopy, requires full bowel preparation, and interpretation of post-treatment findings may be more difficult because of tumour location and the need for complete colonic examination. Nevertheless, extraordinary response rates observed in dMMR colon cancer raise the possibility that organ-preserving strategies may eventually become feasible in carefully selected patients. In the NEOCAP trial, 54% of patients achieved cCR after camrelizumab plus apatinib; of those entering watch-and-wait, 86% were managed non-operatively without regrowth at a median follow-up of 16.4 months [99]. In a phase II study of neoadjuvant pembrolizumab in localised MSI-H/dMMR tumours, overall response rate was 82%, with three-year event-free survival of 80% and overall survival of 94% among patients electing surveillance [105,106]. Data from the extended dostarlimab cohort support the feasibility of non-operative management and, notably, demonstrate that cCR was achieved in 82% of colon cancer patients, with the majority of these electing organ preservation [93]. These early data suggest that non-operative management may be feasible in a substantial proportion of dMMR colon cancers achieving cCR, though longer follow-up and improved multimodal response assessment will be required before this strategy can be adopted as standard practice outside specialised centres.

7.2. Risks of Undertreating Residual Nodal Disease

A distinct question raised by the immunobiology of tumour-draining lymph nodes is whether their early surgical removal might itself compromise the efficacy of immunotherapy. Preclinical evidence indicates that tumour-draining lymph nodes are a principal site of checkpoint-inhibitor-driven T-cell priming and that their disruption markedly attenuates the response to PD-1/PD-L1 blockade [27], which is precisely the rationale for delivering immunotherapy in the neoadjuvant setting, with the nodal basin intact, rather than after resection [31]. It follows that upfront or early lymphadenectomy could in prin-

ciple blunt the expansion of tumour-specific clones and the systemic immune memory on which durable disease control depends [174]. This consideration must, however, be weighed against the established staging and therapeutic value of nodal assessment [89], and on current evidence it remains a biological hypothesis rather than a basis for omitting lymphadenectomy outside trials; the same uncertainty underlies current caution about non-operative management in patients with baseline nodal disease [126]. The “Lymph Node Catalyst” hypothesis proposes that preserved TDLNs may act as immunological reservoirs that enhance responses to immunotherapy but acknowledges that “nodal surgery remains clinically valuable in selected settings, particularly for pathological staging and treatment decision-making” [175]. However, despite high nodal sterilisation rates, residual nodal disease does occur, and current response assessment tools cannot reliably exclude it in the absence of a surgical specimen. In NICHE-2, 14 of 111 patients (13%) had tumour-positive lymph nodes at resection despite high rates of primary tumour regression, and residual nodal disease may persist even when the primary tumour completely regresses pathologically [13]. This challenge is compounded by the aforementioned limitations of response assessment tools, and multimodal assessment provides limited information regarding nodal status, particularly in patients entering non-operative management where no surgical specimen is available. Recurrence events, though rare, have disproportionately involved lymph nodes: in the expanded dostarlimab cohort, four of five recurrences were nodal [93]; in the MD Anderson phase II neoadjuvant pembrolizumab trial, six progression events occurred among thirty-five patients, four of which were salvaged surgically [105].

The heterogeneity of nodal responses within the same lymphatic basin further complicates this picture. Evidence from melanoma demonstrates that non-index nodes may harbour viable tumour (including less responsive clones) despite index node response, with two patients in the OpACIN cohort having 80% viable tumour in non-index nodes while their index lymph node showed partial pathologic response, with the authors explicitly noting the potential for significant recurrence risk had lymphadenectomy been omitted [156]. Asynchronous regression between primary tumours and individual lymph nodes has similarly been documented in non-small-cell lung cancer and head and neck cancer after neoadjuvant checkpoint inhibition [150,152,153], suggesting that nodal response heterogeneity is a consistent feature of immune-mediated regression rather than a tumour-specific phenomenon. Taken together, these observations indicate that neither primary tumour response nor index node status can be reliably used as a surrogate for complete regional nodal clearance. Until validated biomarkers of nodal sterilisation are available, whether circulating tumour DNA (ctDNA)-based, imaging-based, or immunological, complete regional lymphadenectomy remains essential for accurate staging and safe oncological management in resectable dMMR colon cancer outside carefully controlled research settings. The comparative implications for nodal assessment and organ preservation in dMMR colon versus rectal cancer are summarised in Table 3.

Table 3. Comparative implications for nodal assessment and organ preservation in dMMR colon versus rectal cancer.

Feature	Colon Cancer	Rectal Cancer	Key References
Standard staging modality	Contrast-enhanced CT (pooled nodal sensitivity ~71%, specificity ~67%)	Pelvic MRI for locoregional and nodal staging (pooled sensitivity/specificity ~73–74%); CT for distant disease	Nerad et al., 2016 [68]; Shkurti et al., 2023 [70]; Zhuang et al., 2021 [81]; ACR Expert Panel, 2025 [82]

Table 3. Cont.

Feature	Colon Cancer	Rectal Cancer	Key References
Post-treatment response assessment	CT (structural change only; radiologic–pathologic discordance ~64%), supplemented by endoscopy	Multimodal: MRI (T2, DWI/ADC, mrTRG), flexible sigmoidoscopy, digital rectal examination, biopsy; FDG-PET investigational	Xie et al., 2026 [115]; Cao et al., 2023 [113]; Miao et al., 2025 [119]; Amodeo et al., 2018 [122]; Vanderbecq et al., 2026 [124]; Fox et al., 2023 [125]
Endoscopic surveillance	Colonoscopy; full bowel preparation, less well tolerated, interpretation complicated by tumour location	Flexible sigmoidoscopy; better tolerated, direct mucosal visualisation, validated within OPRA	van der Sande et al., 2021 [127]; Williams et al., 2025 [128]; Verheij et al., 2024 [166]
Nodal response assessment	CT only; unreliable, no soft-tissue compartmental equivalent	MRI permits mesorectal and extramesorectal nodal evaluation, though size and morphology remain imperfect; DWI an adjunct	Linhares et al., 2025 [76]; Platt et al., 2023 [77]; Rutegård et al., 2025 [83]; Lunenberg et al., 2026 [84]; Keven et al., 2025 [86]; Hu et al., 2025 [118]
Non-operative management	Investigational; not standard practice; emerging signals (dostarlimab cCR 82% in colon; NEOCAP)	NCCN-recognised option after cCR, within experienced multidisciplinary centres	Cercek et al., 2025 [93]; Yu et al., 2024 [99]; Liao et al., 2026 [112]; NCCN Rectal, 2025 [126]; Petrelli et al., 2025 [167]
Current guideline stance	Neoadjuvant ICI for locally advanced disease (cT4b/bulky nodal); resection with regional lymphadenectomy remains standard	Non-operative management recognised after cCR confirmed by multimodal assessment	NCCN Colon, 2025 [89]; Cercek et al., 2022 [92]; Cercek et al., 2025 [93]; NCCN Rectal, 2025 [126]; Garcia-Aguilar et al., 2022 [165]
Principal barrier to organ preservation	Limited surveillance toolkit (CT plus colonoscopy) relative to the MRI–sigmoidoscopy combination; nodal sterilisation harder to confirm	Nodal compartment still cannot be interrogated without resection; reliance on imaging and endoscopy	Linhares et al., 2025 [76]; Lunenberg et al., 2026 [84]; Vora et al., 2023 [109]; Baucom et al., 2017 [111]; LaPelusa et al., 2025 [106]; Salama et al., 2026 [144]

Abbreviations: ADC, apparent diffusion coefficient; cCR, clinical complete response; CT, computed tomography; DWI, diffusion-weighted imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; mrTRG, MRI tumour regression grade. Supporting evidence and citations are provided in the corresponding prose of Sections 3, 5 and 7.

8. Prognostic Significance of Nodal Response

8.1. ypN Status After Immunotherapy and the Need for Adjuvant Therapy

In conventional colorectal cancer management, pathological lymph node status is one of the strongest predictors of recurrence and survival, guiding decisions regarding adjuvant therapy. The emergence of neoadjuvant immunotherapy introduces a different biological context in which nodal disease may be eradicated through immune-mediated rather than cytotoxic mechanisms, potentially requiring reassessment of the traditional prognostic framework based on ypN status.

The clinical significance of isolated tumour cells and micrometastases persisting within lymph nodes after immunotherapy remains uncertain. Whether microscopic nodal residuals after ICI represent a meaningful disease burden comparable to ypN1 disease in the chemoradiotherapy context, where five-year distant metastasis rates reach 40% for ypN1 and 72% for ypN2 after chemoradiotherapy [176], or whether they are functionally controlled by ongoing systemic immune surveillance, cannot be answered with available data. Evidence from non-small-cell lung cancer suggests that residual nodal burden after

neoadjuvant chemoimmunotherapy carries a clear prognostic gradient [177], but whether this applies after immunotherapy in an inherently immune-sensitive tumour type remains unknown. In contrast, data from melanoma suggest that limited residual viable disease after neoadjuvant checkpoint inhibition may not negatively affect recurrence-free survival, given the durable ongoing efficacy of immune checkpoint inhibitors after cessation of treatment [156].

Evidence from breast cancer further illustrates the complexity: ypN0 and isolated tumour cell or micrometastatic nodal disease carry comparable prognosis after neoadjuvant chemotherapy, while macrometastatic disease confers significantly worse outcomes [178], though the relevance of this distinction in the immunotherapy setting is unresolved. If residual micrometastatic nodal disease after ICI carries a substantially lower recurrence risk than predicted by conventional staging, due to ongoing immune-mediated nodal clearance, this may ultimately support less extensive lymphadenectomy or non-operative surveillance in selected patients. Prospective data with longer follow-up, central histopathological review, and standardised nodal reporting are required. Outside carefully controlled research settings, current NCCN guidelines continue to recommend surgical resection with regional lymphadenectomy for resectable dMMR colon cancer.

These data also raise important questions about the role of adjuvant therapy following neoadjuvant immunotherapy. The ATOMIC trial established that adding atezolizumab to mFOLFOX6 significantly improves three-year disease-free survival in resected stage III dMMR colon cancer (86.4% vs. 76.6%; HR 0.50, 95% CI 0.35–0.72), representing a new standard in the adjuvant setting [90]. However, NCCN guidelines explicitly note that the role of adjuvant immunotherapy following neoadjuvant immunotherapy remains undefined, and real-world data suggest that for patients achieving pCR after neoadjuvant therapy, watchful waiting and adjuvant immunotherapy produce equivalent outcomes. The small subset of patients with residual nodal metastases after ICI may represent a biologically distinct group at higher recurrence risk, in whom adjuvant treatment could remain relevant, but the small numbers of ypN-positive patients across existing cohorts and the limited follow-up duration prevent definitive conclusions. Prospective data with longer follow-up, ideally including central histopathological review and standardised nodal reporting, are required to resolve these questions.

8.2. Long-Term Survival Outcomes

Although long-term data remain limited, early survival outcomes following neoadjuvant immunotherapy appear highly favourable across multiple studies. The PICC trial currently provides the longest available follow-up: at a median of approximately 62 months, no disease recurrence was observed in either treatment group, with five-year overall survival of 100% in the toripalimab plus celecoxib arm and 94% in the toripalimab monotherapy arm, and five-year disease-free survival of 100% and 93%, respectively [104]. In NICHE-2, no recurrences were observed despite inclusion of high-risk tumours including a large proportion of cT4 and node-positive disease [12,13]. In the prospective dostarlimab study, two-year recurrence-free survival was 92% (95% CI 86–99) among more than 100 patients [93]. In a phase II trial of neoadjuvant pembrolizumab for localised dMMR/MSI-H tumours, three-year event-free survival was 80% and overall survival 94%, with patients achieving ctDNA clearance demonstrating markedly superior three-year EFS (92% vs. 20%; $p < 0.001$) [105,106]. These outcomes compare favourably with historical results for stage III dMMR colon cancer treated with adjuvant fluoropyrimidine–oxaliplatin chemotherapy, in which three-year recurrence risks of approximately 35% have been reported, particularly for T4 or N2 disease [179,180]. Meta-analyses of neoadjuvant immunotherapy across solid tumours further support the prognostic importance of deep

pathological response: pCR is associated with improved event-free survival (HR 0.48) and overall survival (HR 0.55), with similar associations reported for major pathological response [181]. Despite these encouraging data, the small number of ypN-positive patients across immunotherapy cohorts and the relatively short follow-up duration mean that the long-term prognostic implications of residual nodal disease after ICI remain incompletely defined.

9. Emerging Technologies and Future Directions

9.1. Circulating Tumour DNA

Among emerging biomarkers, ctDNA has shown particular promise for monitoring treatment response following neoadjuvant immunotherapy. Several studies demonstrate that ctDNA clearance correlates closely with pathological response and may occur earlier than radiologic regression. In the WINDOW trial, which included twenty-four patients with stage II–III dMMR/MSI-H colorectal cancer treated with neoadjuvant tislelizumab, 87.5% achieved two consecutive ctDNA-negative results. Twenty patients subsequently entered a watch-and-wait strategy and, with a median follow-up of 20.3 months, no recurrences occurred, corresponding to an overall complete response rate of 91.7%. Importantly, ctDNA status strongly predicted outcome: the complete response rate was only 25% if ctDNA remained detectable after five treatment cycles, versus 100% among patients achieving ctDNA clearance [182]. In a pilot analysis of localised dMMR/MSI-H colorectal cancer treated with neoadjuvant pembrolizumab, pCR occurred in all six patients without detectable baseline ctDNA compared with four of seven with detectable baseline ctDNA; clearance during treatment was strongly associated with pathological response; and patients without detectable ctDNA after treatment demonstrated markedly improved three-year event-free survival compared with those with persistent ctDNA positivity [106]. Early ctDNA clearance during dostarlimab treatment similarly correlated with sustained cCR and durable disease control [93]. In advanced colorectal cancer treated with ICIs, ctDNA decreased by 83–100% in all responders, including a patient who initially demonstrated radiographic pseudoprogression but subsequently achieved objective response, suggesting that ctDNA may provide an early biological readout when conventional imaging is equivocal [183]. Taken together, these observations suggest that ctDNA could become central to response-adapted treatment strategies, identifying patients suitable for organ preservation, detecting early resistance, and informing optimal treatment duration.

Of particular relevance to nodal staging, ctDNA has been proposed as a potential surrogate marker of nodal sterilisation [13], a clinical need that is currently unmet given the inability of conventional imaging to confirm eradication of lymph node metastases without histological examination of a resected specimen. This proposal must, however, be interpreted with caution. ctDNA reflects whole-body tumour burden and cannot anatomically localise residual disease to the nodal compartment; a negative result does not exclude isolated nodal micrometastases below the detection threshold of current assays [184], and the available data correlate ctDNA dynamics with composite pathological response rather than with nodal status specifically [106]. On present evidence ctDNA therefore cannot replace pathological nodal assessment, and clearance alone should not be taken to confirm regional nodal sterilisation. Should ctDNA clearance in the future be validated against systematic nodal pathology as a reliable indicator of both primary tumour and nodal response, it may help support non-operative management in patients with baseline nodal involvement; prospective validation in adequately powered cohorts with systematic nodal pathological evaluation will, however, be essential before this application can be incorporated into clinical practice [185].

9.2. Tumour Immune Signatures

Beyond ctDNA, tumour immune signatures may provide additional predictive information. In a study of forty-two patients with dMMR colorectal cancer treated with neoadjuvant PD-1 blockade, expression of HLA-DQA1 and HLA-DQB1, together with enrichment of antigen presentation and T-cell receptor signalling pathways, were significantly associated with pCR; higher baseline CD8⁺ T-cell density was also strongly associated with response, with responders demonstrating markedly greater tumour-infiltrating lymphocyte densities than non-responders (767 vs. 326 cells/mm²; $p = 0.013$) [186]. Similar findings have been reported in metastatic disease, where higher tumour-infiltrating lymphocyte counts were associated with improved response rates (70.6% vs. 42.9%; $p = 0.029$) and survival following checkpoint inhibition [187]. Tumours enriched for interferon- γ -related gene signatures, cytotoxic T-cell markers, and antigen-processing machinery demonstrate higher response rates, whereas defects in antigen presentation pathways may contribute to immune resistance [50]. JAK1 frameshift mutations, present in approximately 20% of MSI-H colorectal cancers, are associated with reduced interferon response signatures and transcriptional profiles linked to resistance to anti-PD-1 therapy [21,22]. The spatial organisation of immune cells may also influence treatment response: MSI colorectal cancers demonstrate increased coordinated interactions between Th1, Tc1, and dendritic cells that are largely absent in microsatellite-stable disease, and the presence of TLS within the tumour microenvironment is associated with enhanced antigen presentation, local immune priming, and improved responses to PD-1 inhibition, with high intratumoural TLS scores predicting significantly improved immune-related progression-free survival [15,24–26]. These observations make TLS density an attractive candidate for incorporation into multimodal models of response prediction and patient selection [25]; before this can be realised, however, TLS assessment requires methodological standardisation, encompassing agreement on the quantification approach, the distinction between intratumoural and peritumoural location, and the scoring of maturation state, since these parameters materially affect the prognostic and predictive associations reported and currently preclude direct comparison across studies [188,189]; in colorectal cancer specifically, the prognostic direction of TLS can reverse with location, intratumoural structures associating with favourable and peritumoural structures with adverse outcomes in colorectal liver metastases [138], and a gastrointestinal meta-analysis found the colorectal-specific association with overall survival did not reach significance (HR 0.775, 95% CI 0.570–1.053, $p = 0.103$), attributable in part to this methodological heterogeneity [190], although automated maturation-aware scoring tools now offer a plausible route to reproducible assessment [191]. As multimodal datasets integrating transcriptomics, spatial profiling, and circulating biomarkers become increasingly available, tumour immune signatures may help identify patients most likely to benefit from checkpoint inhibition and guide response-adapted treatment strategies [192] (Figure 6).

9.3. Emerging Imaging Approaches

Functional imaging approaches may also help overcome the limitations of conventional structural imaging. FDG-PET has traditionally been used to identify metabolically active tumour tissue, and early data suggest it may provide complementary information in the immunotherapy setting: in the dostarlimab trial for dMMR rectal cancer, FDG-PET demonstrated early metabolic responses with standardised uptake values declining to background levels even when structural abnormalities persisted on MRI [92]. However, FDG uptake also reflects immune cell infiltration and inflammatory activity, and the influx of lymphocytes and macrophages into the tumour microenvironment following treatment can produce increased uptake that may be misinterpreted as progression [193].

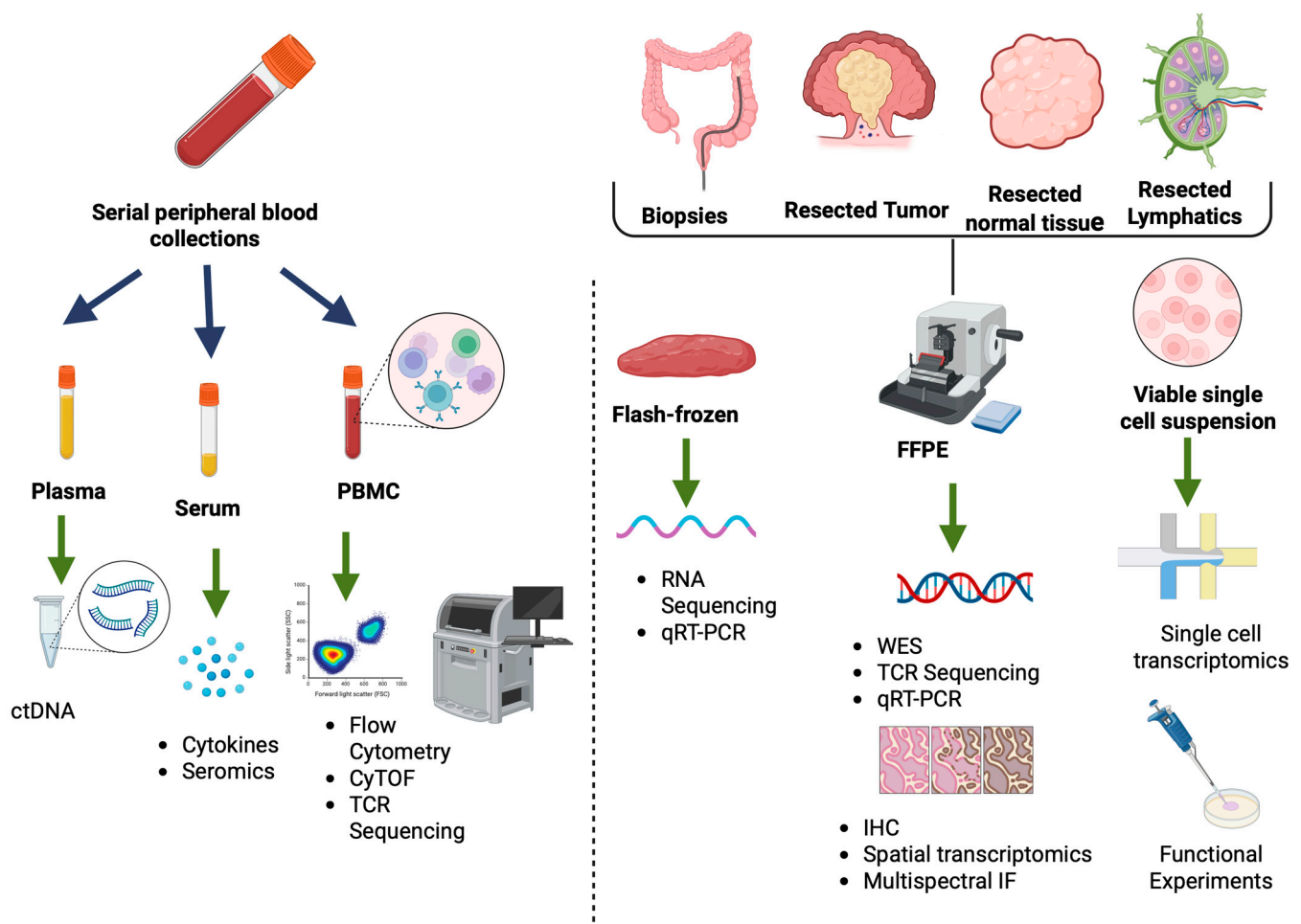


Figure 6. Translational platforms for biomarker discovery in neoadjuvant immunotherapy trials. Neoadjuvant immunotherapy trials increasingly incorporate integrated translational sampling strategies to identify biomarkers of response and resistance. Serial peripheral blood collections allow analysis of circulating tumour DNA (ctDNA), cytokines, and immune cell populations using plasma, serum, and peripheral blood mononuclear cells (PBMCs). These samples can be analysed using techniques including flow cytometry, Cytometry by Time-of-Flight (CyTOF), and T-cell receptor sequencing to characterise systemic immune responses. In parallel, tumour tissue obtained from biopsies and surgical specimens enables genomic, transcriptomic, and spatial profiling. Flash-frozen samples allow RNA sequencing and qRT-PCR analysis, while formalin-fixed paraffin-embedded (FFPE) tissue supports whole-exome sequencing, TCR sequencing, immunohistochemistry, and spatial transcriptomics. Viable tumour and lymph node specimens can also be used for single-cell transcriptomic analysis and functional immune assays. Together, these approaches provide a multidimensional framework for understanding tumour–immune interactions and identifying biomarkers that may guide response-adapted treatment strategies in dMMR colorectal cancer. Created in <https://BioRender.com>.

ImmunoPET, using radiolabelled antibodies or fragments to visualise immune cell populations or checkpoint molecule expression *in vivo*, offers a more specific approach. A first-in-human phase 1 study using ^{18}F -BMS-986192 and ^{89}Zr -nivolumab demonstrated that tumour uptake of both tracers correlated with PD-L1 and PD-1 expression on biopsy and with response to nivolumab [194]. CD8-targeted PET imaging with ^{89}Zr -Df-IAB22M2C has also completed phase 1 trials, with post-treatment tracer uptake in tumour lesions correlating with response in patients with advanced melanoma and hepatocellular carcinoma [134]. A phase 1/2 trial of ^{89}Zr -Df-88082A found that higher SUV was associated with dMMR and longer overall survival, and that uptake was greater in lesions with inflamed than

desert immunophenotypes, revealing substantial heterogeneity in CD8⁺ T-cell distribution within and between patients [133]. A phase 1/2 trial of ⁶⁸Ga-grazytracer PET demonstrated superior predictive value over RECIST for progression-free survival in patients on immunotherapy [195]. These findings raise the possibility of distinguishing immune-mediated nodal enlargement from true metastatic disease. For the nodal compartment specifically, two mechanisms are of particular interest: USPIO-enhanced MRI, which exploits nodal macrophage uptake and therefore reports a biological property of the node rather than its size [196], and CD8- or PD-L1-directed immunoPET, which images the immune activation that underlies nodal flare rather than tumour bulk [197]; combined with serial ctDNA, such approaches may in principle separate immune-mediated nodal enlargement from viable residual deposits, although none has yet been validated for nodal response assessment in dMMR colorectal cancer and all require prospective evaluation against pathological reference standards [198].

USPIO nanoparticle-enhanced MRI may improve nodal characterisation through a different mechanism. Following intravenous injection, USPIO particles are transported to lymph nodes via the lymphatic circulation, where macrophages in healthy nodes phagocytose the particles and produce signal loss on T2-weighted imaging; nodes containing tumour lack this macrophage uptake and maintain high signal [199]. A meta-analysis reported pooled sensitivity of 88–90% and specificity of 96% for detecting nodal metastases across cancer types, significantly outperforming unenhanced MRI [135–137].

Radiomics-based approaches remain largely investigational but show promise. CT radiomic signatures have been shown to predict CD8⁺ immune phenotype and infer clinical outcomes in patients treated with anti-PD-1 or anti-PD-L1 therapy, and to identify pseudoprogression earlier than iRECIST criteria [193]. Delta-radiomics, measuring the relative change in radiomic features between baseline and follow-up imaging, has demonstrated superior predictive performance over pre-treatment radiomics alone, with AUCs of 0.77–0.80 in external validation cohorts for predicting immunotherapy response [139,200,201]. Radiomic analysis has also demonstrated predictive value for lymph node metastasis and pCR specifically in rectal cancer after neoadjuvant therapy [140,141]. An immunophenotype-guided radiomics model specifically developed for neoadjuvant anti-PD-1 response in dMMR/MSI-H colorectal cancer achieved an AUC of 0.904 in independent validation [108].

As multimodal datasets integrating these emerging technologies with ctDNA and tumour immune profiling become available, biologically informed composite response assessment tools may increasingly supplant reliance on structural imaging alone.

10. Unresolved Questions and Clinical Implications

Despite the remarkable activity of immune checkpoint inhibition in dMMR colorectal cancer, several key questions remain unresolved. First, the optimal duration of neoadjuvant immunotherapy has not been established. Trials have used treatment exposures ranging from only a few weeks in NICHE-2 to six months of PD-1 blockade in the dostarlimab programme [13,93], and although deeper responses appear to correlate with longer immune exposure in some patients, the minimal effective duration of therapy has not been defined [202]. Establishing the minimum exposure needed to achieve nodal sterilisation and durable systemic immune memory will be important for balancing efficacy, toxicity, and cost in future treatment protocols.

Second, the clinical significance of residual nodal disease after checkpoint inhibition remains incompletely understood. Because ypN-positive disease is relatively uncommon in immunotherapy cohorts, existing trials have limited statistical power to determine whether residual nodal metastases after ICI carry the same prognostic significance observed

in conventional treatment paradigms. Whether such patients should receive adjuvant chemotherapy, intensified surveillance, or additional immunotherapy cycles is not yet established by prospective evidence.

Third, response assessment remains a major limitation. Conventional imaging frequently underestimates the depth of response because immune-mediated tumour regression produces persistent structural abnormalities that may mimic residual disease. While endoscopic assessment, ctDNA monitoring, and emerging imaging approaches may improve response evaluation, the optimal integration of these modalities into clinical decision-making, including the sequence, frequency, and thresholds for intervention, remains undefined. Standardisation of response assessment criteria across institutions and trials will be essential to enable comparison of outcomes and development of evidence-based management algorithms.

Finally, the role of surgery, and specifically of radical lymphadenectomy and/or resection, in dMMR colorectal cancer may ultimately need to be reconsidered. Immune checkpoint inhibition has already enabled organ preservation in a substantial proportion of rectal cancer patients. Whether similar strategies can be safely extended to colon cancer remains uncertain, particularly given the limitations of current surveillance tools and the difficulty of colonoscopic follow-up compared with the endoscopy–MRI combination available in rectal cancer. More broadly, if biomarkers capable of reliably identifying nodal sterilisation become available, future strategies could incorporate selective surgery or response-adapted lymphadenectomy, an approach that could reduce surgical morbidity in carefully selected patients without compromising oncologic outcomes. Addressing these questions will require prospective trials with longer follow-up, integrated translational research programmes, and standardised approaches to response assessment and nodal evaluation.

11. Conclusions

Neoadjuvant immune checkpoint inhibition has fundamentally reshaped the treatment landscape of dMMR colorectal cancer. Across multiple studies, these therapies produce unprecedented pathological responses and frequent nodal sterilisation, demonstrating that metastatic deposits within regional lymph nodes are highly sensitive to immune-mediated eradication. These observations highlight the central role of TDLNs not only as sites of metastatic dissemination but as critical immunologic organs within the lymphatic system that actively participate in antitumour immune responses, priming tumour-specific T-cell populations and enabling effective systemic immune memory.

At the same time, conventional staging and response assessment frameworks developed for cytotoxic therapies perform poorly in this context. Reactive lymphadenopathy and immune-mediated tissue remodelling frequently produce persistent radiologic abnormalities despite complete tumour clearance, resulting in substantial discordance between imaging and pathological response, a problem that is particularly pronounced in dMMR tumours, where baseline nodal overstaging affects approximately one-third of cases. Accurate interpretation of nodal status therefore requires integrated assessment combining imaging, endoscopy, pathology, and emerging biomarkers, and this multimodal framework will need to evolve as immunotherapy is adopted more broadly across colon and rectal cancer management.

The failure of conventional imaging to accurately capture nodal response after ICI has direct consequences for clinical decision-making. Falsely positive radiologic nodal findings at baseline may inappropriately intensify preoperative treatment; persistent post-treatment nodal abnormalities may discourage organ preservation in patients who have achieved genuine tumour eradication. Closing the gap between imaging and biology, through

ctDNA monitoring, spatial immune profiling, immunoPET, and radiomics, represents a research priority of considerable clinical importance. It bears emphasis, however, that surgical resection with regional lymphadenectomy remains the standard of care for resectable dMMR colon cancer, and that non-operative management of rectal cancer, although now guideline-recognised within experienced centres, presupposes rigorous multimodal confirmation of complete response; the de-escalation of lymphadenectomy, and any extension of organ preservation to colon cancer, are hypotheses requiring prospective validation before they can alter practice. As longer-term data emerge from current and forthcoming trials, a deeper understanding of lymph node immunobiology may ultimately enable selective de-escalation of surgery and lymphadenectomy in patients achieving profound immune-mediated tumour regression, extending the benefits of treatment intensification to a reduction in treatment burden.

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