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Perspective

Neoadjuvant versus Adjuvant Immunotherapy in MSI-H/dMMR Early Colorectal Cancer: A Value-Conscious Re-examination of Dogma

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Abstract

The management of early-stage colorectal cancer (CRC) is undergoing a paradigm shift driven by advances in immunotherapy, particularly for tumors characterized by microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). Representing approximately 15% of non-metastatic CRC, this biologically distinct subgroup is intrinsically resistant to fluoropyrimidine-based chemotherapy yet uniquely sensitive to immune checkpoint inhibition.

This review critically examines the emerging evidence supporting neoadjuvant versus adjuvant immunotherapy strategies in early-stage MSI-H/dMMR colon cancer, drawing on data from FOxTROT, NICHE-2, and ATOMIC. We argue that neoadjuvant immunotherapy is biologically more rational, clinically effective, and value-conscious—particularly relevant in resource-limited settings—while acknowledging that definitive practice change will require randomized comparative trials.

Keywords

- early-stage colorectal cancer
- immunotherapy
- neoadjuvant
- adjuvant
- fluoropyrimidine resistance

Introduction: *When Biology Exposes the Limits of Tradition*

For decades, the management of early-stage colorectal cancer (CRC) followed a predictable sequence: diagnosis, surgery, and adjuvant chemotherapy. Even as molecular heterogeneity became increasingly apparent, treatment paradigms remained largely uniform. Microsatellite instability-high (MSI-H)/mismatch repair deficiency (dMMR) CRC represents one of the clearest examples of this discordance between tumor biology and clinical practice.

MSI-H tumors account for approximately 15% of localized CRCs, with nearly 80% arising sporadically and the remainder associated with Lynch syndrome.[1–4] These tumors are characterized by a high mutational burden, dense lymphocytic infiltration, and increased immune checkpoint expression.[5] Importantly, they are consistently resistant to fluoropyrimidine-based chemotherapy,[6–11] a finding repeatedly confirmed in randomized trials and pooled analyses.

The advent of immune checkpoint inhibitors has not merely added another therapeutic option; it has challenged the foundational sequencing of treatment.[12–14] The key question is no longer whether immunotherapy should be used in MSI-H early CRC, but when it should be deployed for maximal benefit.

Stage II MSI-H Colon Cancer: Observation or Missed Opportunity?

Current guidelines[15,16] recommend observation for stage II MSI-H colon cancer, based on the lack of benefit from adjuvant chemotherapy. While this approach avoids unnecessary toxicity, it leaves approximately 10 to 15% of patients vulnerable to recurrence.

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Notably, stage II patients were well represented in the NICHE-2 trial[12] and demonstrated pathological response rates comparable to those observed in stage III disease. This observation suggests that biological behavior, rather than anatomical stage alone, may better predict benefit from systemic therapy.

Neoadjuvant immunotherapy should not be viewed as a mandate for all stage II MSI-H tumors. Instead, it represents a rational option within clinical trials or shared decision-making frameworks for biologically higher-risk patients.

FOxTROT and the Illusion of Chemotherapy Benefit in MSI-H Disease

The FOxTROT trial[6] established the feasibility of neoadjuvant chemotherapy in operable colon cancer, demonstrating improved downstaging and event-free survival in mismatch repair-proficient tumors. However, outcomes in the MSI-H subgroup were strikingly different.

Pathological tumor regression was observed in only approximately 7% of MSI-H cases, with no meaningful reduction in recurrence. These findings reinforced the biological resistance of MSI-H tumors to fluoropyrimidine-based chemotherapy and should have conclusively discouraged its routine use in this population.

Despite this, oxaliplatin-based adjuvant chemotherapy has continued to be prescribed, reflecting therapeutic inertia rather than evidence-based practice.

Endpoint Selection: Interpreting Early Signals

Several neoadjuvant studies have used 2-year recurrence as a primary endpoint, based on the observation that most relapses in high-risk colon cancer occur within this timeframe. While pragmatic, this endpoint remains a surrogate.

Disease-free survival (DFS) continues to be the globally accepted regulatory endpoint, capturing both recurrence and competing mortality risks. Accordingly, 2-year recurrence should be interpreted as hypothesis-generating rather than practice-defining, underscoring the need for longer-term validation.

Overtreatment Risk and the Imperative of Upfront MMR Testing

A major limitation of chemotherapy-based neoadjuvant strategies is the absence of mandatory upfront MMR testing. Administering neoadjuvant chemotherapy to dMMR tumors delays surgery for a biologically ineffective intervention.

Furthermore, a substantial proportion of patients categorized as "high risk" are ultimately found to have pT3N0 disease, for which chemotherapy is frequently unnecessary. Exposure to avoidable toxicity and surgical delay represents overtreatment rather than therapeutic progress.

This critique applies specifically to chemotherapy-based approaches and highlights why upfront MMR testing must be mandatory rather than optional.

NICHE-2: Proof of Concept for Neoadjuvant Immunotherapy

The NICHE-2 trial[12] evaluated short-course neoadjuvant immunotherapy using ipilimumab and nivolumab in resectable dMMR colon cancer. The results were unprecedented:

- Major pathological response: 95%
- Pathological complete response: 68%
- Timely surgery: 98%
- 3-year DFS: 100%

Responses were consistent across sporadic and Lynch-associated tumors, reinforcing a biology-driven rather than etiology-driven approach. Although NICHE-2 was a single-arm phase II study conducted at expert centers, the magnitude and consistency of benefit make the signal difficult to dismiss (►**Table 1**).

ATOMIC: *Adjuvant Immunotherapy's Best-Case Scenario*

The ATOMIC trial[13] evaluated adjuvant mFOLFOX6 with or without atezolizumab in resected Stage III dMMR colon cancer. The addition of atezolizumab improved 3-year DFS from 76.6 to 86.4%.

However, this benefit came at the cost of mandatory chemotherapy, increased toxicity, prolonged treatment duration, and persistent recurrence in approximately 13% of patients. Favorable outcomes in the control arm likely reflect the inherently good prognosis of dMMR tumors rather than true chemotherapy sensitivity.

Why Neoadjuvant Immunotherapy Outperforms Adjuvant Approaches

The contrast between NICHE-2 and ATOMIC is best explained by biology rather than pharmacology (►**Table 2**). In the neoadjuvant setting, the intact primary tumor serves as a continuous antigen source, facilitating robust T-cell priming and clonal expansion. In the adjuvant setting, this immune amplification is substantially attenuated.

Differences in drug class (PD-1 vs. PD-L1 inhibition) may also contribute, but timing and antigen exposure appear central to the observed disparity.

Why EGFR Antibodies Failed Where Immunotherapy Succeeded

EGFR antibodies have shown limited benefit even in metastatic CRC, largely confined to selected subgroups. In early-stage or micrometastatic disease, their reliance on cytotoxic synergy rather than durable systemic control limits their ability to eradicate residual disease. In contrast, immunotherapy in dMMR tumors exploits intact antigen presentation and immune priming, enabling sustained disease control. This contrast reinforces that treatment success in early-stage CRC is driven by biological context and timing rather than therapeutic escalation.

Table 1 Summary of neoadjuvant chemotherapy versus immunotherapy

Feature	FOxTROT (neoadjuvant chemotherapy)	NICHE-2 (neoadjuvant IO)
Response of MSI-H	Poor	Exceptional (95% major pathological response, 67% pathological complete response)
MSI-low included	Yes	No
Safety and feasibility	Acceptable	Excellent
Trial phase	Phase III	Phase II
DFS (disease-free survival)	No definitive DFS improvement reported in available publications	100% 3-y DFS
HR (hazard ratio)	Not reported	Not estimable (no events)

Abbreviation: MSI-H, microsatellite instability-high.

Table 2 Summary of neoadjuvant versus adjuvant immunotherapy

Feature	NICHE-2 (Neoadjuvant IO)	ATOMIC (Adjuvant IO)
Timing of IO	Before surgery	After surgery
Pathological response	95% major pathological response, 67% pathological complete response	DFS improvement
Chemotherapy included	No	Yes
CRC stage included	I–III	III only
Trial phase	Phase II	Phase III
DFS (disease-free survival)	100% 3-y DFS	Significant DFS improvement
HR (hazard ratio)	Not estimable (no events)	0.58

Abbreviation: CRC, colorectal cancer.

Conclusion

MSI-H/dMMR CRC is uniquely resistant to chemotherapy and uniquely sensitive to immunotherapy. Accumulating evidence supports neoadjuvant immunotherapy as the most biologically rational, clinically effective, and value-conscious strategy in early-stage disease.

While randomized comparative trials are still needed, the burden of proof increasingly rests with proponents of prolonged adjuvant approaches. For MSI-H/dMMR colon cancer, the question is no longer whether immunotherapy should be used—but whether delaying it represents a missed opportunity.

Patient Consent

Patient consent is not required due to the retrospective nature of the study.

Conflict of Interest

None declared.

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