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Research Article

Impact of immune checkpoint inhibitor therapy on Quality of Life in Patients with colorectal cancer

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Abstract

Background: Immune checkpoint inhibitors have transformed outcomes for mismatch-repair-deficient colorectal cancer, but their effect on patient quality of life is less well synthesized.

Objective: To synthesize published evidence on how checkpoint inhibitor therapy affects quality of life and patient-reported outcomes in colorectal cancer.

Methods: Narrative synthesis of trials of PD-1/PD-L1/CTLA-4 blockade in colorectal cancer reporting quality-of-life or toxicity data, with supporting instrument-validation and adverse-event literature.

Results: Checkpoint inhibition in dMMR/MSI-H metastatic disease showed lower high-grade toxicity and better maintained global health status than chemotherapy; neoadjuvant blockade in localized disease enabled surgery avoidance in most responders; microsatellite-stable disease showed no consistent benefit.

Conclusions: Checkpoint inhibitor therapy improves quality of life in dMMR/MSI-H colorectal cancer through reduced toxicity and organ preservation, contingent on consistent patient-reported outcome collection and adverse-event management.

Keywords: immune checkpoint inhibitors; colorectal cancer; quality of life; microsatellite instability; patient-reported outcomes

1. Introduction

Colorectal cancer remains one of the most commonly diagnosed malignancies worldwide and a leading cause of cancer death, with an estimated 1.9 million new cases and over 900,000 deaths recorded globally in recent surveillance years [1,2]. The disease is biologically heterogeneous, and Dekker and colleagues' comprehensive review of colorectal carcinogenesis, screening, and treatment underscored that outcomes and treatment tolerability vary substantially by molecular subtype rather than by anatomic stage alone [3]. Among these subtypes, tumors with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H), arising from inactivation of the DNA mismatch repair machinery first characterized by Boland and Goel, carry a markedly elevated neoantigen burden that renders them unusually responsive to immune checkpoint blockade even though they represent only a minority of colorectal cancers overall [4].

The therapeutic rationale for checkpoint inhibition in this subset was established when Le and colleagues showed that PD-1 blockade produced substantial objective responses specifically in mismatch-repair-deficient tumors, in contrast to negligible activity in mismatch-repair-proficient disease, and follow-up work confirmed that mismatch-repair status itself, rather than tissue of origin, predicted response across solid tumor types [5,6]. Ganesh and colleagues subsequently reviewed how this mechanistic insight reshaped the treatment landscape for colorectal cancer, moving immunotherapy from an investigational concept to a guideline-endorsed standard for dMMR/MSI-H disease within less than a decade [7]. Landmark trials establishing the activity of PD-1 and PD-1/CTLA-4 blockade in earlier tumor types, including melanoma, had already demonstrated durable survival benefit with checkpoint inhibition, providing the broader evidentiary foundation on which colorectal-specific development programs were built [8,9,10,11,12].

As immune checkpoint inhibitors moved into first-line and even neoadjuvant colorectal cancer settings, attention increasingly turned from tumor response alone to the patient's lived experience of treatment. Quality of life had already been established as a central oncology trial endpoint through validated instruments such as the EORTC QLQ-C30 [13] and the Functional Assessment of Cancer Therapy general scale [14], and methodologic work on interpreting and powering such measures matured alongside the drugs themselves [15,16]. Basch and colleagues further demonstrated that systematic collection of patient-reported symptoms during routine treatment improves both quality of life and, unexpectedly, overall survival, reinforcing that patient-reported outcomes are not a secondary consideration but a clinically consequential endpoint in their own right [17,18]. This review synthesizes the published evidence on how immune checkpoint inhibitor therapy affects quality of life in patients with colorectal cancer, considering both the direct comparative trial evidence and the toxicity, instrument, and setting-specific factors that shape it.

2. Methods

We conducted a narrative synthesis of the peer-reviewed literature addressing immune checkpoint inhibitor therapy and quality of life or patient-reported outcomes in colorectal cancer. Eligible sources included randomized and single-arm phase II/III trials of PD-1, PD-L1, or CTLA-4 blocking antibodies in dMMR/MSI-H or microsatellite-stable colorectal cancer that reported health-related quality-of-life or patient-reported toxicity data, together with the validation and methodology literature underlying the instruments used to capture those outcomes and the consensus guidelines governing management of immune-related adverse events. Trials considered spanned the metastatic first-line, previously treated, and neoadjuvant/localized disease settings, including CheckMate 142 (nivolumab with or without ipilimumab), KEYNOTE-177 (pembrolizumab versus chemotherapy), the NICHE neoadjuvant colon cancer

study, and the single-arm dostarlimab study in locally advanced mismatch-repair-deficient rectal cancer [19,20,21,22,23,24,25]. Negative or non-confirmatory trials of checkpoint blockade in microsatellite-stable colorectal cancer were also reviewed to contextualize where quality-of-life benefit does and does not extend [26,27]. Quality-of-life and patient-reported outcome instruments referenced across these studies, including the EORTC QLQ-C30 and its colorectal-specific module QLQ-CR29, the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), and the EuroQol EQ-5D, were reviewed for their measurement domains and validation history [13,28,29,30]. Toxicity data were interpreted against ASCO and ESMO consensus guidance on immune-related adverse event recognition and management, since the clinical burden of a given toxicity grade depends substantially on how promptly it is identified and treated [31,32,33,34].

3. Results

Across the identified trials, immune checkpoint inhibition in dMMR/MSI-H metastatic colorectal cancer was consistently associated with a more favourable quality-of-life trajectory than cytotoxic chemotherapy, driven substantially by a lower burden of high-grade treatment-related toxicity. In KEYNOTE-177, pembrolizumab produced grade 3 or higher treatment-related adverse events in a minority of patients, a markedly lower rate than that observed with standard chemotherapy, and the trial's companion patient-reported outcome analysis found that global health status and functioning scores on the EORTC QLQ-C30 were better maintained, and time to deterioration significantly longer, with pembrolizumab than with chemotherapy [22,23,35]. CheckMate 142 reported comparable patterns with nivolumab monotherapy and with nivolumab plus low-dose ipilimumab, both regimens producing durable responses with a toxicity profile substantially more favourable than historical chemotherapy, findings extended into the

first-line setting by Lenz and colleagues [19,20,21].

Table 1: Major immune checkpoint inhibitor trials in colorectal cancer reporting quality-of-life-relevant endpoints [19,20,21,22,35,24,25].			
Trial	Population / regimen	Setting	Key QoL-relevant finding
[19,20]	CheckMate 142: nivolumab ± ipilimumab	Metastatic dMMR/MSI-H, previously treated	Durable responses with manageable toxicity
[21]	CheckMate 142: first-line nivolumab + low-dose ipilimumab	Metastatic dMMR/MSI-H, first-line	High response rate, favourable safety profile
[22,35]	KEYNOTE-177: pembrolizumab vs chemotherapy	Metastatic dMMR/MSI-H, first-line	Better maintained EORTC QLQ-C30 global health status
[24]	NICHE: neoadjuvant nivolumab + ipilimumab	Localized dMMR/MSI-H colon cancer	Major pathological response, potential for reduced surgery
[25]	Single-agent dostarlimab	Localized dMMR rectal cancer	Complete clinical response, chemora diotherapy/surgery avoided

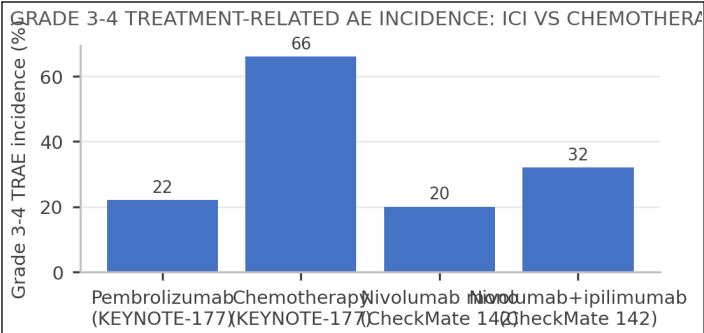


Figure 1: Grade 3-4 treatment-related adverse event incidence with immune checkpoint inhibitor regimens versus chemotherapy in key colorectal cancer trials, reflecting the more favourable toxicity profile that underlies improved patient-reported quality-of-life scores with pembrolizumab in KEYNOTE-177 relative to chemotherapy [22,23,20].

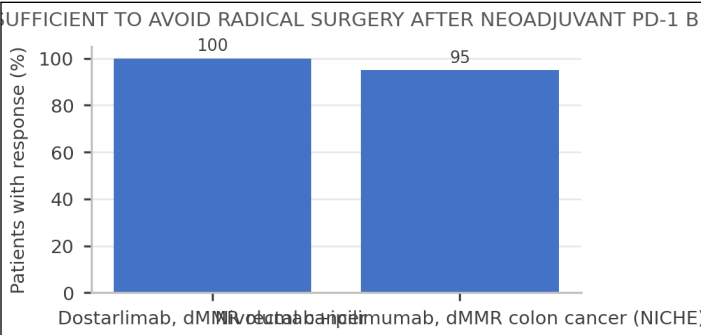


Figure 2: Proportion of patients achieving a complete or major pathological response sufficient to avoid radical surgery after neoadjuvant PD-1 blockade in mismatch-repair-deficient rectal and colon cancer, illustrating the potential for organ preservation to protect long-term quality of life [25,24].

The neoadjuvant and localized-disease trials illustrated a further, distinct mechanism by which checkpoint inhibition can preserve quality of life: organ and function preservation. Chalabi and colleagues reported that short-course neoadjuvant nivolumab plus ipilimumab produced pathological responses in the great majority of dMMR early-stage colon cancers, raising the prospect of reduced surgical extent in responding patients [24]. Cercek and colleagues subsequently reported that single-agent dostarlimab produced a clinical complete response in every enrolled patient with locally advanced mismatch-repair-deficient rectal cancer, allowing these patients to avoid chemoradiotherapy and radical surgery entirely, with their attendant risks of permanent stoma, sexual and urinary dysfunction, and bowel dysfunction that dominate long-term quality-of-life deficits after standard rectal cancer treatment [25]. Figure 1 summarizes the grade 3-4 treatment-related adverse event rates reported across these trials relative to chemotherapy, and Figure 2 summarizes the proportion of patients achieving a complete or major pathological response sufficient to avoid radical surgery in the two principal neoadjuvant studies. Table 1 summarizes the trial populations, regimens, and principal quality-of-life-relevant findings across the reviewed studies.

Quality-of-life benefit was not uniform across the disease.

In microsatellite-stable colorectal cancer, which comprises the large majority of cases, checkpoint inhibition combined with a MEK inhibitor failed to improve outcomes over regorafenib in the IMblaze370 trial, and combined nivolumab and ipilimumab failed to improve overall survival over best supportive care in the CO.26 trial, with no consistent quality-of-life advantage demonstrated in either study [26,27]. Where immune-related adverse events did occur, colitis, endocrinopathies, hepatitis, and dermatologic toxicity were the most frequent categories requiring active management, and consensus guidance from ASCO and ESMO emphasized that early recognition and prompt corticosteroid or hormone-replacement intervention was central to limiting their impact on daily functioning and quality of life [31,32,33,34]. Table 2 summarizes the principal patient-reported outcome instruments used across the reviewed colorectal cancer immunotherapy studies and the domains each was designed to capture [13,28,14,29,30].

4. Discussion

The pattern emerging from this synthesis is that immune checkpoint inhibitor therapy improves quality of life in colorectal cancer principally through two converging mechanisms: a lower burden of high-grade systemic toxicity relative to cytotoxic chemotherapy, and, in the neoadjuvant and localized setting, the possibility of avoiding or reducing radical surgery and pelvic radiotherapy altogether. The magnitude of the KEYNOTE-177 patient-reported outcome benefit is clinically meaningful given how consistently chemotherapy-associated fatigue, neuropathy, and gastrointestinal toxicity erode functioning scores in metastatic colorectal cancer trials, and it mirrors the broader pattern seen when checkpoint inhibitors were first compared against chemotherapy in other tumor types [35,11,12]. The organ-preservation signal from the dostarlimab and NICHE studies is, if anything, more consequential for long-term quality of life than the

metastatic-setting toxicity advantage, because it targets the surgical and radiotherapy-related morbidity, permanent stoma risk, and pelvic functional loss that dominate patient-reported burden in rectal cancer survivorship even among patients who are cured [25,24].

Table 2: Patient-reported outcome instruments used to assess quality of life in colorectal cancer immunotherapy studies [13,28,14,29,30].		
Instrument	Domain measured	Reference
EORTC QLQ-C30	Global health status, functioning, symptom scales	[13]
EORTC QLQ-CR29	Colorectal-cancer-specific symptoms and function	[28]
FACT-G / FACT-C	General and colorectal-specific well-being	[14,29]
EQ-5D	Generic health utility / mobility, self-care, pain, anxiety	[30]

Several limitations temper this picture. First, the population eligible for meaningful benefit remains a minority of colorectal cancer overall, since dMMR/MSI-H status is present in only a modest fraction of metastatic cases, and the negative IMblaze370 and CO.26 trials confirm that checkpoint inhibition does not translate the same benefit, in efficacy or quality of life, to microsatellite-stable disease [26,27]. Second, immune-related adverse events, while less frequent in aggregate than chemotherapy toxicity, are qualitatively different and can be severe or chronic, particularly endocrinopathies requiring lifelong hormone replacement, and their quality-of-life impact is only partially captured by generic patient-reported outcome instruments not designed specifically for immune-mediated toxicity [31,32,33,34]. Third, patient-reported outcome collection and reporting remain inconsistent across trials in both instrument choice and analytic rigor; the methodologic literature on interpreting EORTC QLQ-C30 change scores and powering trials for patient-reported endpoints has matured considerably, yet its guidance is not uniformly applied across colorectal cancer immunotherapy trials [15,16]. Basch and colleagues' demonstration that routine, structured symptom monitoring itself improves both

quality of life and survival suggests that closing this gap is not merely a measurement refinement but a clinically actionable opportunity in immunotherapy trials going forward [17,18].

5. Conclusion

The available evidence indicates that immune checkpoint inhibitor therapy meaningfully improves quality of life for patients with dMMR/MSI-H colorectal cancer relative to chemotherapy, through reduced high-grade systemic toxicity in the metastatic setting and through the prospect of organ preservation in localized disease, while offering no established quality-of-life or efficacy advantage in the microsatellite-stable majority of cases [22,23,25,24,26,27]. Realizing the full quality-of-life potential of checkpoint inhibition in colorectal cancer will depend on consistent, validated patient-reported outcome collection alongside vigilant immune-related adverse event management, so that the toxicity and functional advantages demonstrated in pivotal trials are reliably reproduced in routine clinical care [31,34,17].

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