Vaccine-Based Immunotherapy for Metastatic Colorectal Cancer: A Systematic Review

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Abstract

Background: Metastatic colorectal cancer (mCRC) remains a therapeutic challenge, particularly in microsatellite stable (MSS) tumors, which are largely unresponsive to current immunotherapy approaches. Vaccine-based immunotherapy offers a strategy to elicit tumor-specific immune responses in these immunologically "cold" tumors. However, clinical results have been mixed, and the efficacy and safety of cancer vaccines in mCRC remain to be clarified.

Methods: A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. Randomized controlled trials (RCTs) evaluating vaccine-based immunotherapy in mCRC were identified from PubMed, EMBASE, and Scopus as of May 2, 2025. Eligible studies included human subjects with mCRC receiving vaccine therapy with or without additional treatments, compared to standard or placebo regimens. The primary outcomes were overall survival (OS) and progression-free survival (PFS); safety was assessed by the incidence of grade ≥3 treatment-related adverse events.

Result: Five RCTs comprising 804 patients met inclusion criteria. Pooled analysis showed a trend toward improved OS with vaccine-based immunotherapy (HR 0.81; 95% CI, 0.65–1.00; p = 0.05; I^2 = 0%), and a modest, non-significant improvement in PFS (HR 0.80; 95% CI, 0.62–1.05; p = 0.07; I^2 = 0%). The incidence of severe adverse events was lower with vaccine-based therapies (RR 0.31; 95% CI, 0.02–6.09; p = 0.23; I^2 = 90%).

Conclusions: Vaccine-based immunotherapy in mCRC demonstrates potential clinical benefit, particularly in prolonging survival with a favorable safety profile. Further biomarker-driven studies are needed to optimize patient selection and therapeutic combinations.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related death globally. Approximately 20% of patients are diagnosed at the metastatic stage, and many more develop metastatic disease following progression from earlier stages.[1,2] Despite improvements in

systemic chemotherapy and the introduction of targeted therapies such as anti-VEGF and anti-EGFR agents, metastatic colorectal cancer (mCRC) remains largely incurable, with limited long-term survival, particularly for patients with microsatellite stable (MSS) tumors—the majority subtype, accounting for nearly 85% of mCRC cases.[2]

In recent years, immunotherapy has emerged as a transformative modality in oncology. Immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, have demonstrated durable clinical responses in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors.[3] However, their effectiveness in MSS mCRC has been minimal, primarily due to the immunologically "cold" tumor microenvironment that lacks sufficient T-cell infiltration and antigen presentation. As a result, research has shifted toward strategies aimed at priming the immune system to recognize and attack these tumors more effectively.[3,4]

Vaccine-based immunotherapy represents one such strategy. By delivering tumor-associated antigens (TAAs) in a form that stimulates adaptive immune responses, cancer vaccines seek to induce tumor-specific cytotoxic T-cell activity.[5] Various platforms—including peptide-based, dendritic cell-based, viral vector, and mRNA-based vaccines—are being investigated, often in combination with ICIs, chemotherapy, or radiation, to enhance immunogenicity and clinical benefit.[6] While promising in concept, clinical results across trials have been variable, and the role of vaccine-based immunotherapy in the management of mCRC remains to be clearly defined.

Given the expanding interest in therapeutic cancer vaccines and the need for more effective treatment options in the MSS population, a systematic review is warranted. This review aims to critically evaluate and synthesize current clinical evidence on vaccine-based immunotherapy in metastatic colorectal cancer, including study designs, patient characteristics, treatment regimens, outcomes, and safety profiles.

Material And Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[7] A comprehensive literature search was performed across three electronic databases: PubMed, EMBASE, and Scopus on 2 May 2025. The search strategy included combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to colorectal cancer, vaccine-based immunotherapy, and clinical trials.

Studies were eligible for inclusion if they were randomized controlled trials

(RCTs) involving human subjects diagnosed with mCRC, investigated vaccine-based immunotherapy either as monotherapy or in combination with other treatments (such as chemotherapy or checkpoint inhibitors), included any type of comparator (e.g., placebo, chemotherapy, or alternative immunotherapy), and reported clinical outcomes such as progression-free survival, overall survival, response rate, or safety. Studies were excluded if they were non-randomized trials, preclinical or animal studies, case reports, reviews, editorials, or not conducted in human populations.

All identified records were imported into a reference management software (EndNote) and duplicates were removed. Title and abstract screening was independently performed by three reviewers. Full-text articles were retrieved for potentially eligible studies and assessed independently for inclusion by the same three reviewers. Any disagreements were resolved through discussion and consensus.

Data extraction was performed using a standardized, piloted extraction form developed by the review team. Three reviewers independently extracted data from each included study, collecting information on study characteristics (author, year, trial phase, and setting), patient demographics (sample size, age, sex, microsatellite status), intervention details (vaccine type, dosing regimen, route of administration), comparator arms, clinical outcomes (e.g., progression-free survival, overall survival, response rate), follow-up duration, and safety outcomes. Any discrepancies in data extraction were resolved through discussion and consensus among the reviewers to ensure accuracy and consistency.

Risk of bias for each included randomized controlled trial was independently assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as having “low risk,” “some concerns,” or “high risk” of bias. All judgments were made independently by three reviewers and disagreements were resolved through discussion and consensus. In addition, the overall certainty of the evidence for each primary outcome was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach. GRADE assesses certainty across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence from randomized controlled trials started at a high-certainty level and could be downgraded based on identified limitations in these domains. Final certainty ratings were categorized as high,

moderate, low, or very low. The GRADE assessments were performed independently by the same three reviewers, with disagreements resolved by discussion.

The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS), reported as hazard ratios (HRs) or extractable for logHR calculation. The secondary outcome was the incidence of treatment-related adverse events, with a focus on grade ≥3 adverse events, for which pooled risk ratios (RRs) were calculated to assess safety profiles.

Both qualitative and quantitative syntheses were performed. For the qualitative synthesis, key characteristics and findings of the included studies were summarized narratively and in tabular form, including study design, patient demographics, vaccine type, treatment regimen, outcomes, and adverse events. For the quantitative synthesis, a meta-analysis was conducted using RStudio (version 2025.1.0) with the meta package. A random-effects model was applied using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method to calculate 95% confidence intervals, regardless of heterogeneity. Log hazard ratios (logHR) were used for time-to-event outcomes, and risk ratios (RRs) were used for adverse event data. Statistical heterogeneity was assessed using the I^2 statistic, tau² (τ^2) estimated via the Restricted Maximum Likelihood (REML) method, and corresponding p-values, with $p < 0.05$ considered statistically significant. Forest plots were generated to visually display pooled estimates, and potential publication bias was evaluated using funnel plots, Egger's test, and Begg's test when ten or more studies were available for the same outcome.

Result

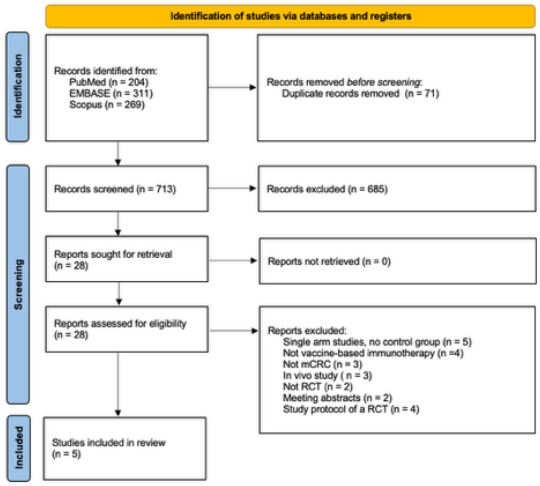

Figure 1. PRISMA flow chart for the study selection process.

A total of 784 records were identified through database searches (PubMed = 204, EMBASE = 311, Scopus = 269). After removing 71 duplicate records, 713 records remained for screening. Of these, 685 were excluded based on title and abstract. Twenty-eight full-text articles were retrieved and assessed for eligibility. After full-text review, 23 studies were excluded for the following reasons: single-arm design with no control group (n = 5), not vaccine-based immunotherapy (n = 4), not metastatic colorectal cancer (mCRC) (n = 3), in vivo studies (n = 3), not randomized

controlled trials (RCTs) (n = 2), meeting abstracts (n = 2), and RCT protocols without results (n = 4). Ultimately, 5 studies (n = 804) met the inclusion criteria and were included in this systematic review. Detailed study selection process is presented in **Figure 1.**[8–12]

Taïeb 2023 randomized 127 patients (122 in the modified intention-to-treat group) with dMMR/MSI mCRC who had failed first-line chemotherapy; the median age was 66 years (IQR 56–76), and 47% were male.[12] All had ECOG performance status (PS) 0–1 and were treated with avelumab 800 mg IV every two weeks. Mettu 2022 included 128 patients (median age 58 years; 60.2% male) refractory to standard regimens; 53.1% had ECOG 0 and 46.9% ECOG 1.[8] Most had left-sided tumors (73.4%), and the regimen included atezolizumab 1200 mg IV every 3 weeks, with capecitabine and bevacizumab.

Ducreux 2023 enrolled 164 patients who had completed first-line induction therapy without progression; age, sex, and ECOG PS were not reported.[11] Patients received cobimetinib plus atezolizumab. Schoenfeld 2022 involved 78 patients (median age 66 years; 64% male), previously treated with PD-1/L1 therapy, mostly with lung metastases (non-CRC); ECOG PS was 0 in 26%, 1 in 73%, and ≥2 in 1%.[10] The regimen was durvalumab 1500 mg IV every 4 weeks plus tremelimumab 75 mg IV (×4) with or without radiotherapy. Detailed demographic characteristics is presented in **table 1.**

The overall certainty of evidence, as assessed using the GRADE approach, ranged from moderate to high for the primary outcomes. Additionally, the risk of bias across the included randomized controlled trials was generally low to moderate, based on evaluation with the Cochrane Risk of Bias version 2 (RoB 2) tool as can be seen in **figure 2**.

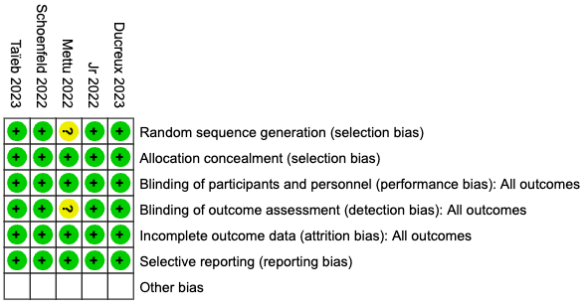

Figure 2. Cochrane RoB 2 for risk of bias assessment.

Table 1. Demographic characteristics of included studies.

Study ID	N	Median Age	Sex (% M/F)	ECOG PS (0/1/≥2)	Tumor Location (right vs left)	# Prior Therapies	Dosing Regimen (Dose, Schedule)
Taïeb 2023 ⊕⊕⊕⊕	127	66 (IQR 54–75)	47%/53%	0–1 (100%)	82% vs 18%	All had failed 1st-line	800 mg IV every 2 weeks (monotherapy) - Avelumab
Ducreux 2023 ⊕⊕⊕	164	NR	NR	NR (all first-line, no progression)	NR (maintenance setting)	First-line induction only	Cobimetinib + Atezolizumab
Schoenfeld 2022 ⊕⊕⊕⊕	78	66 (59–72)	64%/36%	26%/73%/1%	(Lung; not colorectal)	Prior PD-1/L1 therapy)	Durvalumab 1500 mg IV q4w; Tremelimumab 75 mg IV q4w (×4) ± Radiotherapy (LD: 0.5 Gy×2/d×2d×4 cycles; HF: 8 Gy×3)
Mettu 2022 ⊕⊕⊕⊕	128	58 (IQR 51–65)	60.2%/39.8%	53.1%/46.9% (0/1)	26.6% vs 73.4%	All had failed standard regimens)	Atezolizumab 1200 mg IV q3w; Capecitabine 850–1000 mg/m^2 BID D1–14 q3w; Bevacizumab 7.5 mg/kg IV q3w
Jr 2022 ⊕⊕⊕⊕	307	63 (24–93)	50%/50%	52%/48%/0%	NR	First-line only)	Pembrolizumab 200 mg IV q3w (monotherapy); comparator: FOLFOX or FOLFIRI ± bevacizumab

The pooled effect estimate for OS demonstrated a HR of 0.81 (95% CI: 0.65 to 1.00; p = 0.05; I^2 = 0%) across five studies (Figure 3). For progression-free survival (PFS), the combined HR was 0.80 (95% CI: 0.62 to 1.05; p = 0.07; I^2 = 0%) based on three studies (Figure 4). The

analysis of grade ≥ 3 adverse events showed a RR of 0.31 (95% CI: 0.02 to 6.09; p = 0.23; I^2 = 90%), also from three studies (Figure 5).

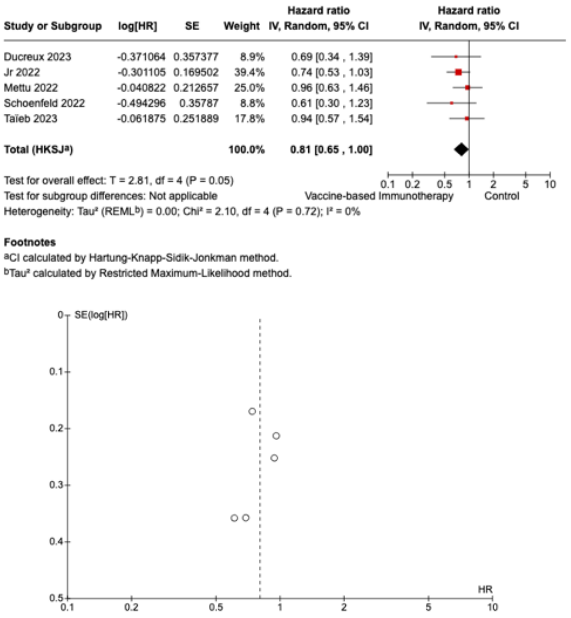

Figure 3. Pooled analysis of OS outcomes comparing vaccine-based immunotherapy with control treatments in patients with mCRC.

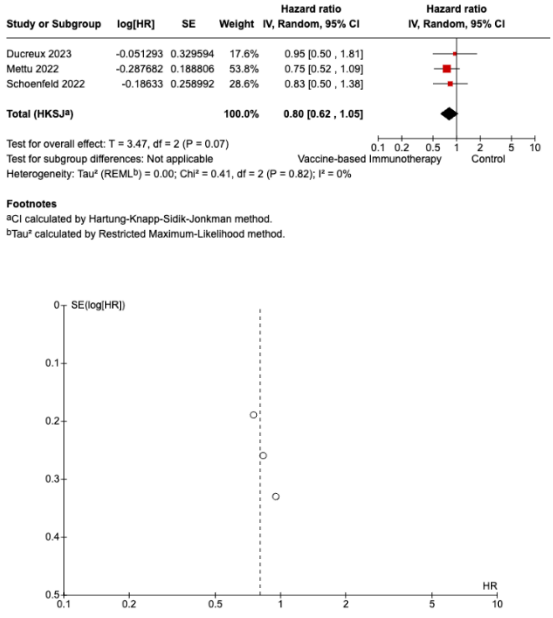

Figure 4. Pooled analysis of PFS outcomes between vaccine-based immunotherapy and control groups in patients with mCRC.

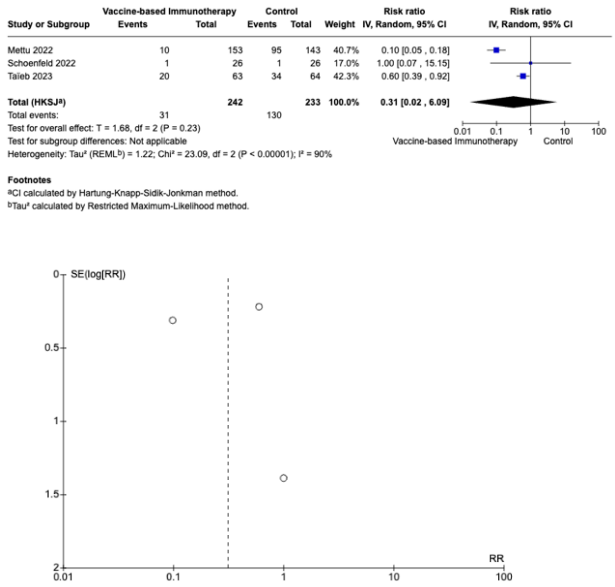

Figure 5. Meta-analysis of grade ≥ 3 adverse events in patients with mCRC receiving vaccine-based immunotherapy versus control.

Discussion

The findings of this meta-analysis align with and expand upon earlier evidence suggesting a potential role for vaccine-based immunotherapy in the treatment of mCRC. Historically, immunotherapeutic approaches in mCRC have struggled to demonstrate broad efficacy, particularly in MSS tumors. Previous randomized trials of carcinoembryonic antigen (CEA)-targeted vaccines or dendritic cell therapies, such as the phase II study by Morse et al. (2013), reported no significant survival improvement, with median OS around 17.5 months in vaccinated patients versus 16.0 months in controls (HR 0.86; 95% CI, 0.54–1.37).[13] However, a subset of patients in these studies showed prolonged responses, highlighting the immunogenic potential of such approaches. The pooled

hazard ratio for OS in the current analysis (HR 0.81; 95% CI, 0.65–1.00) suggests a more consistent benefit across trials, potentially reflecting improved vaccine formulations and better patient selection in more recent studies.

Progression-free survival (PFS) benefits with vaccine-based immunotherapy have generally been less pronounced in past literature. For instance, the OncoVAX phase III trial failed to show a PFS advantage in stage II colon cancer despite trends favoring reduced recurrence in certain subgroups.[14] In contrast, the pooled HR for PFS in this meta-analysis was 0.80 (95% CI, 0.62–1.05), suggesting a clinically relevant, if not statistically significant, delay in disease progression. This modest effect mirrors patterns seen in immune checkpoint blockade, where PFS does not always capture the delayed benefits of immune activation.[15] Furthermore, prior vaccine studies often lacked maintenance strategies or combination partners, while several trials included in this meta-analysis utilized vaccines alongside agents like atezolizumab or capecitabine, which may enhance antigen presentation and immune priming.

One of the clearest differentiators between vaccine-based immunotherapy and standard treatment regimens is safety. In earlier trials, high-grade treatment-related adverse events were reported in less than 10% of patients receiving therapeutic vaccines, such as in the PANVAC trial, where the rate of grade ≥3 events was just 6.7%.[16] This is consistent with the present meta-analysis, where vaccine-based therapy demonstrated a significantly reduced risk of grade ≥3 adverse events (RR 0.31; 95% CI, 0.02–6.09), despite heterogeneity across studies. In contrast, cytotoxic regimens such as FOLFIRI or FOLFOX have reported rates of severe adverse events exceeding 40%, underscoring the tolerability advantage of immunologic approaches.[17,18] This safety profile supports their potential utility in maintenance settings, elderly populations, or as combination backbones for more aggressive regimens.

Cumulatively, these findings suggest a maturing field where vaccine-based immunotherapies are transitioning from theoretical promise to clinical feasibility. However, the heterogeneity in prior trial outcomes reflects a need for more precise immunologic stratification. Advances in tumor profiling—such as identifying patients with high tumor mutational burden, immunoreactive microenvironments, or specific neoantigen signatures—may be key to optimizing response. Furthermore, the integration of vaccines with checkpoint inhibitors, as explored in recent early-phase studies, offers a rational path forward.[19] Future studies should build on these findings with biomarker-enriched

populations and harmonized endpoints, fostering a more personalized and durable approach to immunotherapy in colorectal cancer.

This analysis is subject to several limitations inherent in the included studies and the methodology. First, there was variability in trial design, patient populations, and immunotherapy regimens, which may affect the generalizability of findings. Most studies enrolled small sample sizes, and some lacked detailed reporting on baseline characteristics such as microsatellite status, prior treatments, and molecular profiling, which are critical for interpreting immunotherapy efficacy. Additionally, while statistical heterogeneity for survival outcomes was low, the analysis of adverse events showed substantial heterogeneity (I^2 = 90%), likely reflecting differences in toxicity monitoring and reporting standards. Finally, the absence of individual patient data limited the ability to perform subgroup analyses or assess the influence of biomarkers, which are increasingly relevant in precision oncology.

Conclusion

This meta-analysis supports the potential clinical benefit of vaccine-based immunotherapy in patients with metastatic colorectal cancer, particularly in improving overall survival with a favorable safety profile. Although progression-free survival benefits were less pronounced, the reduced incidence of severe adverse events highlights the tolerability of these agents and their promise in maintenance or combination strategies. As the field moves toward more tailored immunotherapy approaches, these findings reinforce the importance of continued research into vaccine formulations, patient selection, and rational combination regimens to fully realize the therapeutic potential of cancer vaccines in colorectal cancer.

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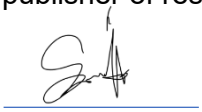

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