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Effectiveness and safety of HIPEC for colorectal peritoneal metastasis: a systematic review

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 September 2026 and was last updated on 8 September 2026.

INTRODUCTION

Review question / Objective Population: Patients aged ≥18 years with advanced colorectal cancer (CRC), stratified into two clinical settings: (1) therapeutic setting—patients with established peritoneal metastasis (CRC-PM); (2) prophylactic/adjuvant setting—patients with high-risk locally advanced CRC (e.g., T4 or perforated) without established PM.

Intervention: Hyperthermic intraperitoneal chemotherapy (HIPEC) administered via intraperitoneal perfusion at ≥41°C for ≥30 minutes, with various chemotherapeutic agents (oxaliplatin, mitomycin C, fluorouracil, etc.), either combined with cytoreductive surgery (CRS) or systemic chemotherapy.

Comparison: Control groups receiving no HIPEC, including CRS alone, systemic chemotherapy alone, routine surveillance, or palliative care.

Outcomes: Primary outcome—overall survival (OS); secondary outcomes—disease-free survival (DFS)/progression-free survival (PFS), peritoneal metastasis (PM) rate, and adverse events (AEs).

Study design: Randomized controlled trials (RCTs) published in English or Chinese.

Objective: To systematically evaluate the efficacy and safety of HIPEC for advanced CRC through a meta-analysis of RCTs, with prespecified stratification by clinical setting (therapeutic vs. prophylactic/adjuvant) to provide robust evidence for clinical decision-making regarding HIPEC use in CRC-PM and high-risk locally advanced CRC patients.

Condition being studied Colorectal cancer (CRC) is a grave disease worldwide, representing the second leading cause of cancer-related mortality globally. Peritoneal metastasis (PM) is a major challenge in the management of CRC, with approximately 5%–15% of CRC cases already presenting with PM at the time of diagnosis, and 20% of patients developing secondary PM after curative surgery. CRC-PM is associated with a particularly poor prognosis and remains a significant clinical challenge despite aggressive multimodal treatment.

This systematic review focuses on two distinct clinical settings of advanced CRC: (1) Therapeutic setting—patients with established peritoneal metastasis originating from CRC (CRC-PM); (2) Prophylactic/Adjuvant setting—patients with high-risk locally advanced CRC without established PM (e.g., T4 stage, perforated colon cancer, or those at high risk of peritoneal recurrence). These two entities represent fundamentally distinct biological contexts, disease burdens, and therapeutic objectives, and thus require separate evaluation.

METHODS

Participant or population Patients aged ≥18 years with advanced colorectal cancer (CRC), categorized into two distinct clinical settings:

1. Therapeutic setting: Patients with established peritoneal metastasis (PM) originating from CRC (CRC-PM), regardless of prior treatment history.

2. Prophylactic/Adjuvant setting: Patients with high-risk locally advanced CRC without established PM at initial surgery, including but not limited to:

Stage T4 tumors

Perforated colon cancer

Other conditions at high risk of peritoneal recurrence (e.g., high N stage)

No restrictions were placed on gender, ethnicity, or disease duration. Studies involving patients with PM from non-CRC primary tumors were excluded. Patients with extraperitoneal distant metastases were also excluded.

Intervention Hyperthermic intraperitoneal chemotherapy (HIPEC), defined as the intraperitoneal perfusion of chemotherapeutic agents at a temperature ≥41°C for a continuous duration of ≥30 minutes. HIPEC may be administered:

In combination with cytoreductive surgery (CRS) — either concurrently or sequentially

In combination with systemic chemotherapy

As a standalone procedure (e.g., second-look surgery + HIPEC)

Commonly used HIPEC chemotherapeutic agents in the included studies include:

Oxaliplatin (360–460 mg/m^2)

Mitomycin C (30–35 mg/m^2)

Fluorouracil (400 mg/m^2–2 g)

Cisplatin (200 mg/m^2)

Irinotecan (200 mg/m^2)

Perfusion temperature is generally maintained at 41–44°C, and perfusion duration ranges from 30 to 90 minutes. No restrictions were placed on drug type, dosage, or perfusion protocol, as the review aims to evaluate HIPEC as a broad therapeutic modality.

Comparator Control groups receiving no HIPEC, which may include: (1) cytoreductive surgery (CRS) alone; (2) systemic chemotherapy alone (e.g., FOLFOX6, XELOX regimens); (3) routine surveillance/monitoring; (4) palliative surgery combined with systemic chemotherapy; or (5) standard care without HIPEC. Studies in which the control group received other regional intraperitoneal therapies (e.g., EPIC or PIPAC) were excluded. No restrictions were placed on the specific type of non-HIPEC control treatment, as the primary comparison of interest is HIPEC versus any non-HIPEC regimen.

Study designs to be included Only randomized controlled trials (RCTs) were included. No restrictions were placed on blinding (open-label trials were eligible), publication status, or sample size. Studies published in English or Chinese were considered. Non-RCTs (including cohort studies, case-control studies, case series, reviews, commentaries, letters, conference abstracts, and ongoing trials without final results) were excluded.

Eligibility criteria Additional inclusion criteria:

Studies reporting at least one of the following outcomes: overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), peritoneal metastasis (PM) rate, or adverse events (AEs)

Full-text availability

Additional exclusion criteria:

Studies with insufficient or unobtainable statistical data for meta-analysis (e.g., no extractable OR, HR, or event counts)

Repeated publications (only the most recent or most comprehensive version included)

Studies where the control group received other regional intraperitoneal therapies (e.g., EPIC, PIPAC)

Studies in which either the treatment or control group had undergone prior HIPEC

Animal studies, in vitro studies, and basic mechanistic research without clinical outcome data.

Information sources A comprehensive systematic search was conducted across the following electronic databases from inception to May 31, 2026 (searched on June 2, 2026):

English-language databases:

PubMed

Embase

Web of Science

Cochrane Library

Chinese-language databases:

China National Knowledge Infrastructure (CNKI)

Wanfang Data

VIP (Chongqing VIP Chinese Science and Technology Periodical Database)

Additional sources:

Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies.

Grey literature was not systematically searched.

No contact with study authors was made for unpublished data.

Clinical trial registries were not searched, as only completed RCTs with final published results were eligible for inclusion.

Main outcome(s) Primary outcome:

Overall survival (OS), defined as the time from randomization to death from any cause or last follow-up. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were prioritized for time-to-event analysis. When HRs were unavailable, binary survival rates at fixed time points (1-, 2-, 3-, and 5-year survival) were pooled as odds ratios (ORs) with 95% CIs as an exploratory alternative.

Timing: Assessment at 1, 2, 3, and 5 years post-randomization (or post-surgery, depending on study reporting).

Effect measures: HR (preferred) or OR with 95% CI.

Quality assessment / Risk of bias analysis The risk of bias of the included randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2.0). The evaluation comprised five domains:

Risk of bias arising from the randomization process

Risk of bias due to deviations from the intended interventions

Risk of bias due to missing outcome data

Risk of bias in measurement of the outcome

Risk of bias in selection of the reported result

Each domain was rated as "low risk," "some concerns," or "high risk." The overall risk of bias for each study was determined based on the domain-level assessments. Two independent reviewers conducted the assessments separately, and any discrepancies were resolved through discussion or consultation with a third reviewer.

For outcome-level assessment, objective endpoints (e.g., OS, DFS) and subjective/safety endpoints (e.g., adverse event grading) were evaluated separately, recognizing that open-label

surgical designs may introduce measurement bias for subjective outcomes.

Results were visualized using risk of bias plots and summary charts generated with RevMan 5.3 software.

Strategy of data synthesis Meta-analyses were performed using RevMan 5.3 software.

Effect measures:

For time-to-event survival outcomes (OS, DFS/PFS): Hazard ratios (HRs) with 95% confidence intervals (CIs) were prioritized.

For dichotomous variables (survival rates, DFS rates, PM incidence, and AEs incidence): Odds ratios (ORs) with 95% CIs were used.

Heterogeneity assessment:

Statistical heterogeneity was assessed using the I^2 statistic and the Chi^2 test (significance threshold: $P < 0.10$).

If I^2 0.10, a fixed-effects model (Mantel-Haenszel method) was applied.

If $I^2 \geq 50\%$ or $P \leq 0.10$, a random-effects model (DerSimonian-Laird method) was applied.

Stratified analyses:
Prespecified stratified analyses were conducted for all efficacy outcomes according to clinical setting:

Therapeutic CRC-PM trials (patients with established PM at baseline)

Prophylactic/Adjuvant HIPEC trials (high-risk CRC patients without established PM)

Sensitivity analysis:
Sensitivity analyses were planned to investigate the impact of study quality, missing data, and clinical heterogeneity on the pooled results.

Subgroup analyses:
Due to the limited number of included studies, prespecified subgroup analyses (e.g., by HIPEC drug type, perfusion duration) could not be performed.

Other:
All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Subgroup analysis Prespecified stratified analyses (primary subgrouping):

The following stratified analyses were prespecified for all efficacy outcomes according to clinical setting:

Therapeutic CRC-PM trials: Studies enrolling patients with established peritoneal metastasis (PM) at baseline.

Prophylactic/Adjuvant HIPEC trials: Studies enrolling high-risk locally advanced colorectal cancer patients without established PM (e.g., T4 stage, perforated colon cancer).

Exploratory subgroup analyses (planned but not feasible due to limited study numbers):

By HIPEC chemotherapeutic agent (oxaliplatin vs. mitomycin C vs. others)

By HIPEC perfusion duration (short vs. prolonged)

By peritoneal cancer index (PCI) score (low vs. high, if consistently reported)

Note: Due to the limited number of included studies for each outcome, the planned subgroup analyses by drug type, perfusion duration, and PCI score could not be performed. Only the prespecified stratification by clinical setting (therapeutic vs. prophylactic/adjuvant) was feasible.

Sensitivity analysis Sensitivity analyses were planned and conducted to investigate the robustness of the pooled results and to explore potential sources of clinical and methodological heterogeneity. The following sensitivity analyses were prespecified:

Study quality: Excluding studies assessed as having "some concerns" or "high risk" on the RoB 2.0 tool to evaluate the impact of methodological quality on pooled effect estimates.

Heterogeneity: Exploring the impact of applying alternative statistical models (fixed-effects vs. random-effects) when heterogeneity was borderline (I^2 near 50%).

Clinical heterogeneity: Examining the influence of variations in HIPEC protocols (e.g., drug type, perfusion duration, temperature) and patient characteristics (e.g., T stage, N stage) on the pooled results, where data permitted.

Note: Due to the limited number of included studies and sparse outcome reporting across trials, formal sensitivity analyses (e.g., leave-one-out meta-analysis) could not be comprehensively performed. The primary sensitivity approach was the prespecified stratification by clinical setting (therapeutic vs. prophylactic/adjuvant) to address clinical heterogeneity. The results should be interpreted with caution given the limited statistical power for sensitivity testing.

Country(ies) involved China.

Keywords colorectal cancer, peritoneal metastasis, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, randomized controlled trial, meta-analysis.

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