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Colorectal Peritoneal Metastases: Prognostic Stratification, Cytoreductive Surgery, Intraperitoneal Treatment Strategies, and Long-Term Oncological Outcomes

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ABSTRACT

Colorectal peritoneal metastases represent a challenging manifestation of advanced colorectal cancer, characterized by heterogeneous tumor distribution, limited therapeutic accessibility, and

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Review International Science Journal

variable oncological outcomes. Advances in cytoreductive surgery and intraperitoneal treatment strategies have transformed the management of selected patients; however, controversies persist regarding surgical eligibility, the additional benefit of hyperthermic intraperitoneal chemotherapy (HIPEC), and the optimal integration of systemic therapies. This narrative review critically examines international scientific evidence concerning patient selection, prognostic determinants, cytoreductive surgery, intraperitoneal therapeutic approaches, and oncological outcomes, incorporating the Latin American perspective. Evidence from randomized clinical trials, observational studies, systematic reviews, prognostic investigations, and international consensus recommendations was evaluated through a descriptive and comparative analytical framework. The findings identified completeness of cytoreduction, peritoneal tumor burden, anatomical resectability, and selected clinical and molecular characteristics as important determinants of survival. The PRODIGE 7 trial demonstrated comparable median overall survival following cytoreductive surgery with and without oxaliplatin-based HIPEC (41.7 versus 41.2 months), while severe postoperative adverse events at 60 days were more frequent in the combined-treatment group (26% versus 15%). Prognostic meta-analyses consistently associated incomplete cytoreduction and increasing Peritoneal Cancer Index with unfavorable survival outcomes. Emerging approaches, including pressurized intraperitoneal aerosol chemotherapy, demonstrated preliminary clinical activity, although their long-term survival benefits remain uncertain. Latin American institutional experience highlighted regional advances alongside persistent differences in access to specialized oncological care. Overall, the evidence supports individualized patient selection, complete macroscopic cytoreduction when feasible, and multidisciplinary treatment planning as fundamental principles of management. Further prospective investigations are required to clarify the role of alternative intraperitoneal regimens, integrate molecular prognostic models, and improve oncological outcomes across diverse healthcare settings.

KEYWORDS

colorectal peritoneal metastases, colorectal cancer, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, HIPEC, peritoneal cancer index, patient selection, oncological outcomes, pressurized intraperitoneal aerosol chemotherapy, survival, surgical oncology, Latin America

INTRODUCTION

Colorectal cancer remains a major global health challenge, particularly when metastatic dissemination compromises the effectiveness of conventional treatment strategies. Among the different patterns of metastatic spread, colorectal peritoneal metastases (CRPM) represent a particularly complex clinical condition, associated with reduced survival, progressive abdominal symptoms, and substantial deterioration in quality of life. Historically, peritoneal involvement was considered a manifestation of advanced, largely incurable disease, with therapeutic options predominantly limited to systemic chemotherapy and palliative interventions. However, advances in surgical oncology, perioperative care, and locoregional therapies have progressively transformed this perspective, allowing selected patients to achieve prolonged survival through multidisciplinary treatment strategies [1], [15], [20].

Cytoreductive surgery (CRS) has emerged as a central component of treatment for carefully selected patients with CRPM. Its primary objective is the complete removal of visible peritoneal tumor deposits through extensive surgical procedures, including peritonectomy and visceral resections when necessary. Early clinical investigations demonstrated encouraging survival outcomes when CRS was combined with hyperthermic intraperitoneal chemotherapy (HIPEC), establishing the foundation for specialized peritoneal surface oncology programs. The randomized trial conducted by Verwaal et al. demonstrated improved survival with combined locoregional treatment compared with the conventional therapeutic approaches available at that time. Subsequent multicenter investigations reinforced the potential benefits of aggressive surgical management, particularly when complete macroscopic cytoreduction could be achieved [4], [5], [9].

Nevertheless, the success of CRS depends considerably on appropriate patient selection. The Peritoneal Cancer Index (PCI), which quantifies the anatomical distribution and extent of peritoneal disease, constitutes a fundamental prognostic tool. Higher PCI scores, extensive small bowel involvement, and the inability to achieve complete cytoreduction are generally associated with unfavorable outcomes. Additional factors, including performance status,

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
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Review International Science Journal

nutritional condition, histological characteristics, and the presence of extraperitoneal metastases, influence surgical eligibility and postoperative prognosis. Systematic reviews and prognostic models have emphasized the importance of integrating these variables rather than relying exclusively on tumor burden, supporting individualized decision-making within experienced multidisciplinary teams [10]–[12].

Molecular characterization has introduced new perspectives into the selection and management of patients with CRPM. Alterations involving the RAS/RAF signaling pathway, microsatellite instability, and other tumor-associated molecular features may influence disease progression, systemic treatment response, and long-term survival. Emerging investigations have also explored relationships between colorectal cancer molecular subtypes and sensitivity to intraperitoneal chemotherapeutic agents. Although these findings remain insufficient to establish definitive molecular criteria for surgical selection or HIPEC regimen choice, they highlight the importance of incorporating tumor biology into conventional anatomical and clinical assessment [13], [14].

Despite the growing acceptance of CRS in selected patients, the additional benefit of HIPEC remains controversial. The PRODIGE 7 randomized phase III trial demonstrated that adding a specific short-duration oxaliplatin-based HIPEC regimen to complete or near-complete cytoreduction did not significantly improve overall survival compared with CRS alone. These findings prompted international reassessment of intraperitoneal chemotherapy protocols and strengthened interest in alternative approaches, particularly mitomycin C-based regimens. Recent recommendations from the Peritoneal Surface Oncology Group International emphasize the need to distinguish the oncological value of complete cytoreduction from the uncertain incremental effectiveness of different HIPEC protocols [2], [3], [18].

Other therapeutic strategies have also been investigated to improve disease control and expand treatment possibilities. Perioperative systemic chemotherapy may contribute to the management of occult metastatic disease and facilitate assessment of tumor responsiveness before surgery. Meanwhile, pressurized intraperitoneal aerosol chemotherapy (PIPAC) has emerged as an investigational approach for patients with unresectable peritoneal metastases, although its effects on long-term survival require further clarification. Randomized trials evaluating prophylactic HIPEC and second-look surgery have additionally demonstrated the importance of distinguishing preventive interventions from therapeutic approaches for established metastatic disease [6]–[8], [16], [17].

From an international perspective, treatment availability and outcomes are also influenced by institutional experience, surgical expertise, healthcare resources, and access to multidisciplinary oncology services. Although much of the published evidence originates from European and other high-volume international centers, Latin American institutions have progressively contributed to the development of specialized programs. Reports from the Latin American Registry of Peritoneal Diseases document regional experience with CRS and HIPEC, emphasizing the importance of evaluating these strategies across different healthcare settings. Such participation is essential for understanding treatment applicability, institutional variability, and opportunities to strengthen collaborative research within Latin America [1], [19].

Considering the evolving evidence, several questions remain clinically relevant: which patients derive the greatest survival benefit from CRS, what criteria should guide surgical eligibility, and under which circumstances might intraperitoneal therapies provide additional oncological advantages? Accordingly, **the objective of this narrative review is to critically examine contemporary evidence regarding patient selection for cytoreductive surgery, the role of intraperitoneal therapeutic strategies, and oncological outcomes in colorectal peritoneal metastases**, incorporating international findings and the Latin American perspective. Through a thematic synthesis of randomized clinical trials, observational studies, systematic reviews, and international consensus recommendations, this article seeks to identify established therapeutic principles, persistent controversies, and priorities for future clinical investigation.

DEVELOPMENT

Clinical and Prognostic Assessment of Colorectal Peritoneal Metastases

The management of colorectal peritoneal metastases (CRPM) requires an individualized approach that considers both the anatomical distribution of metastatic deposits and the biological characteristics of the primary malignancy. Unlike isolated hepatic or pulmonary metastases, peritoneal dissemination frequently involves multiple abdominal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

compartments, complicating complete tumor removal and limiting the effectiveness of conventional systemic treatment. Consequently, therapeutic decisions must balance the expected oncological benefit against surgical morbidity, functional deterioration, and the probability of disease recurrence [1], [15], [20].

The Peritoneal Cancer Index (PCI) is among the most widely used instruments for evaluating disease extent and surgical feasibility. It categorizes tumor involvement across 13 abdominopelvic regions, producing a score between 0 and 39. Although lower PCI values generally correlate with improved survival, the anatomical distribution of metastatic deposits remains equally relevant. Extensive small bowel or mesenteric involvement may prevent complete cytoreduction even in patients with relatively moderate PCI scores. Hallam et al. and Narasimhan et al. identified tumor burden, completeness of cytoreduction, and adverse pathological characteristics as important determinants of postoperative survival, reinforcing the importance of comprehensive preoperative evaluation [10], [11].

Patient selection must additionally incorporate performance status, nutritional condition, comorbidities, previous oncological treatment, and the presence of extraperitoneal metastases. Molecular alterations involving KRAS, NRAS, and BRAF, together with microsatellite instability status, contribute further prognostic information. Although molecular profiling is increasingly relevant in metastatic colorectal cancer, its specific application to surgical eligibility remains under investigation. Integrating molecular and clinical variables into validated prognostic models may improve the identification of patients most likely to benefit from extensive locoregional treatment [12]–[14].

Cytoreductive Surgery and Surgical Completeness

Cytoreductive surgery (CRS) constitutes the principal potentially curative locoregional treatment for selected patients with resectable CRPM. The procedure seeks to eliminate all visible peritoneal metastases through a combination of peritonectomy, tumor excision, and visceral resections when required. Its effectiveness depends strongly on achieving complete macroscopic cytoreduction, conventionally classified as CC-0, indicating the absence of visible residual tumor. In selected treatment protocols, CC-1 cytoreduction, representing residual deposits measuring no more than 2.5 mm, has also been evaluated, although residual disease may adversely influence prognosis [1], [9].

Evidence from multicenter observational studies demonstrates that complete cytoreduction is consistently associated with favorable survival outcomes compared with incomplete tumor removal. Elias et al., in an analysis involving 523 patients, documented the clinical relevance of disease extent and surgical completeness in determining long-term prognosis. Similarly, randomized investigations comparing aggressive locoregional treatment with conventional therapeutic strategies established the potential survival advantages of surgical management in appropriately selected populations [4], [5], [9].

Nevertheless, CRS is associated with substantial operative complexity. Anastomotic leakage, intra-abdominal infection, hemorrhage, thromboembolic events, and prolonged postoperative recovery remain clinically relevant complications. Surgical eligibility must therefore reflect not only the technical possibility of tumor removal but also the probability of preserving acceptable postoperative function and quality of life. Multidisciplinary evaluation within experienced centers is essential to minimize preventable complications and avoid procedures unlikely to provide meaningful oncological benefit [1], [11].

Intraperitoneal Chemotherapy and Therapeutic Controversies

Hyperthermic intraperitoneal chemotherapy (HIPEC) was developed to complement CRS by exposing residual microscopic disease to concentrated regional chemotherapy under controlled hyperthermic conditions. The theoretical advantages include increased local drug exposure and potentially enhanced cytotoxic activity. However, substantial differences in chemotherapy agents, perfusion duration, temperature, and drug concentrations have complicated the standardization of this intervention [2], [18].

The PRODIGE 7 randomized phase III trial represented a turning point in evaluating the clinical effectiveness of HIPEC. Among 265 patients, median overall survival was 41.7 months following CRS combined with oxaliplatin-based HIPEC and 41.2 months following CRS alone, without a significant survival difference. Furthermore, grade 3 or higher complications at 60 days occurred in 26% and 15% of patients, respectively. These findings demonstrated

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

that the investigated HIPEC regimen did not provide additional survival benefits and was associated with increased late postoperative morbidity [3].

However, these results should not be interpreted as definitive evidence against every intraperitoneal chemotherapy protocol. International consensus recommendations have distinguished the unfavorable findings associated with short-duration, high-dose oxaliplatin HIPEC from the unresolved effectiveness of alternative regimens. Mitomycin C-based protocols remain under consideration in selected settings, although the supporting evidence is limited and further comparative studies are required [2], [18].

Other intraperitoneal strategies, particularly pressurized intraperitoneal aerosol chemotherapy (PIPAC), are being investigated for unresectable disease. Early clinical trials have demonstrated feasibility and evidence of pathological treatment response, although their small sample sizes and nonrandomized designs prevent definitive conclusions regarding survival improvement. Accordingly, PIPAC remains an investigational approach rather than an established substitute for complete surgical cytoreduction [16], [17].

Systemic Treatment and Oncological Outcomes

Systemic chemotherapy remains an essential component of multidisciplinary management, particularly for patients with unresectable disease, unfavorable tumor biology, or suspected microscopic systemic dissemination. Contemporary treatment strategies may incorporate fluoropyrimidines, oxaliplatin, irinotecan, and selected targeted agents according to molecular characteristics and previous treatment exposure. Nevertheless, peritoneal metastases remain associated with an unfavorable prognosis in many patients receiving systemic treatment alone [15].

Perioperative chemotherapy has been proposed to improve disease control and facilitate evaluation of tumor responsiveness before surgery. The randomized phase II investigation conducted by Rovers et al. supported the feasibility of incorporating perioperative systemic therapy into the management of resectable CRPM. However, uncertainties remain regarding the optimal treatment sequence, the duration of chemotherapy, and its definitive effect on overall survival [8].

Oncological outcomes must be interpreted through several complementary indicators, including overall survival, progression-free survival, recurrence patterns, postoperative morbidity, and functional recovery. The survival results observed in highly selected surgical cohorts cannot be generalized to all patients with peritoneal dissemination because disease burden, tumor biology, and surgical eligibility differ considerably. Furthermore, the occurrence of peritoneal recurrence after apparently complete cytoreduction demonstrates that macroscopic tumor clearance does not necessarily eliminate microscopic residual disease [3], [9], [10].

International Evidence and the Latin American Perspective

International recommendations increasingly emphasize centralized multidisciplinary management, standardized surgical assessment, and careful evaluation of the evidence supporting intraperitoneal treatment. Nevertheless, access to specialized procedures remains uneven across healthcare systems, particularly in regions where institutional resources, surgical training, and oncological infrastructure vary considerably [1], [20].

Latin America has contributed to the development of peritoneal surface oncology through collaborative research and specialized surgical programs. The Latin American Registry of Peritoneal Diseases reported participation from 76 centers across eight countries, representing 248 surgeons and institutional experience involving 2,682 patients treated with CRS and HIPEC for different peritoneal malignancies. Although these findings were not restricted to colorectal cancer, they demonstrated substantial regional experience and identified the importance of harmonizing therapeutic indications, treatment protocols, and institutional practices [19].

Strengthening multicenter registries, improving access to specialized surgical training, and promoting prospective clinical investigations could facilitate the generation of regionally representative evidence. From this perspective, the future management of CRPM should emphasize not only the refinement of surgical and pharmacological techniques but also equitable access to multidisciplinary assessment, standardized outcome reporting, and the development of therapeutic strategies adapted to diverse healthcare environments [1], [19], [20].

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

General Objective

To critically analyze and synthesize current international scientific evidence regarding patient selection for cytoreductive surgery, the clinical application of intraperitoneal therapies, and oncological outcomes in colorectal peritoneal metastases, integrating anatomical, molecular, prognostic, and therapeutic factors to establish an evidence-based framework for multidisciplinary decision-making, with particular consideration of clinical practices and research developments in Latin America.

Specific Objectives

Cognitive Domain

- **Identify and describe** the principal pathophysiological mechanisms, clinical characteristics, and prognostic factors associated with colorectal peritoneal metastases, emphasizing their influence on disease progression and therapeutic planning.
- **Analyze and differentiate** the indications, benefits, limitations, and complications of cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, and emerging intraperitoneal treatments based on contemporary scientific evidence.
- **Evaluate and compare** oncological outcomes reported in randomized clinical trials, systematic reviews, and observational studies, considering overall survival, disease recurrence, postoperative morbidity, and completeness of cytoreduction.

Psychomotor Domain

- **Outline and organize** the practical steps required for systematic assessment of surgical eligibility, including interpretation of the Peritoneal Cancer Index, anatomical distribution of metastatic deposits, and criteria for complete cytoreduction.
- **Develop and structure** an evidence-based clinical decision-making framework that illustrates the sequential evaluation of patients with colorectal peritoneal metastases, integrating diagnostic findings, surgical feasibility, and therapeutic alternatives. This procedural framework is intended for educational application rather than direct assessment of clinical technical skills.

Affective Domain

- **Recognize and value** the importance of multidisciplinary collaboration, informed patient participation, and individualized risk–benefit assessment when considering complex oncological interventions.
- **Promote and critically appraise** principles of ethical clinical decision-making, equitable access to specialized oncological care, and international scientific cooperation, emphasizing the inclusion of Latin American experiences in the development of comprehensive treatment strategies.

OBJECT OF STUDY

The object of study of this review is the clinical and oncological management of colorectal peritoneal metastases (CRPM), with particular emphasis on patient selection for cytoreductive surgery (CRS), the therapeutic role of intraperitoneal chemotherapy, and the factors influencing postoperative and long-term oncological outcomes. This clinical condition represents a distinct pattern of metastatic colorectal cancer characterized by tumor dissemination throughout the peritoneal cavity, resulting in heterogeneous disease distribution, variable biological behavior, and considerable therapeutic complexity [1], [20].

The population of interest comprises adult patients diagnosed with histologically confirmed colorectal adenocarcinoma and synchronous or metachronous peritoneal metastases, regardless of sex or geographic origin. Particular attention is

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

directed toward patients evaluated for potentially complete surgical cytoreduction, as well as individuals with unresectable disease who may benefit from alternative systemic or investigational locoregional strategies. Evidence from international clinical populations is considered alongside published Latin American experiences to identify similarities and differences in therapeutic practices and healthcare accessibility [9], [15], [19].

The principal variables examined include the Peritoneal Cancer Index, completeness of cytoreduction, tumor histology, molecular characteristics, performance status, associated comorbidities, and previous systemic treatment. Therapeutic interventions of interest encompass CRS, hyperthermic intraperitoneal chemotherapy (HIPEC), perioperative systemic chemotherapy, and pressurized intraperitoneal aerosol chemotherapy (PIPAC). These interventions are evaluated according to their reported indications, limitations, safety profiles, and potential contributions to disease control [2], [8], [10], [16].

The outcomes of interest include overall survival, progression-free survival, recurrence patterns, postoperative complications, treatment-related mortality, and quality of life when reported in the available literature. The analysis also considers how institutional experience, multidisciplinary coordination, and access to specialized oncological services influence the feasibility and implementation of treatment strategies [3], [11], [19].

The scope of this study is limited to the critical examination and synthesis of previously published scientific evidence. It does not involve direct patient recruitment, experimental interventions, or the collection of original clinical data. Accordingly, its purpose is to establish a structured understanding of the relationship between patient characteristics, treatment selection, and oncological outcomes, identifying areas of clinical consensus, unresolved controversies, and priorities for future investigation.

METHODOLOGY

Study Design

This study was structured as a descriptive and analytical narrative literature review, adopting a systematic scientific inquiry framework to examine contemporary evidence regarding colorectal peritoneal metastases (CRPM). The methodological approach integrates principles of the scientific method, including problem identification, formulation of research questions, evidence evaluation, comparative analysis, and interpretation of published findings.

A narrative review design was selected because the available literature encompasses heterogeneous clinical investigations, including randomized controlled trials, observational cohorts, systematic reviews, prognostic studies, and international consensus statements. This approach permits the integration of surgical, pharmacological, molecular, and prognostic perspectives without assuming that the included studies are sufficiently homogeneous for quantitative meta-analysis.

Research Questions and Analytical Framework

The central research question was formulated as follows: *How do patient selection criteria, cytoreductive surgery, and intraperitoneal therapeutic strategies influence oncological outcomes in adults with colorectal peritoneal metastases?*

Three complementary questions guided the analytical framework: which clinical and biological characteristics are associated with favorable outcomes following cytoreductive surgery; what evidence supports the use of HIPEC and emerging intraperitoneal therapies; and how do international clinical recommendations compare with published experiences from Latin American institutions?

The research framework was organized around the Population, Intervention, Comparison, and Outcomes (PICO) model. The population comprised adults with colorectal peritoneal metastases. Interventions included cytoreductive surgery, HIPEC, perioperative systemic therapy, and PIPAC. Comparisons included alternative treatment regimens, surgery without HIPEC, systemic treatment alone, or other relevant therapeutic approaches when reported. Outcomes included overall survival, progression-free survival, recurrence, postoperative morbidity, mortality, and quality of life.

Sources of Information and Search Strategy

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The bibliographic framework prioritized peer-reviewed scientific literature indexed in PubMed/MEDLINE and journals represented in Scopus, with additional consideration of international consensus documents and multicenter research reports. Searches were organized around combinations of controlled vocabulary and free-text expressions relevant to peritoneal surface oncology.

The principal search terms included *colorectal cancer*, *colorectal peritoneal metastases*, *peritoneal carcinomatosis*, *cytoreductive surgery*, *hyperthermic intraperitoneal chemotherapy*, *peritoneal cancer index*, *patient selection*, *oncological outcomes*, *perioperative chemotherapy*, and *pressurized intraperitoneal aerosol chemotherapy*.

An illustrative reproducible PubMed search strategy is presented below:

("Colorectal Neoplasms"[MeSH] OR "colorectal cancer"[Title/Abstract]) AND ("peritoneal metastases"[Title/Abstract] OR "peritoneal carcinomatosis"[Title/Abstract]) AND ("cytoreductive surgery"[Title/Abstract] OR "HIPEC"[Title/Abstract] OR "intraperitoneal chemotherapy"[Title/Abstract] OR "patient selection"[Title/Abstract])

The literature framework emphasized publications from 2003 through October 2026, allowing the inclusion of foundational clinical trials alongside more recent therapeutic developments. Studies from different geographic regions were considered, including relevant contributions from Latin America.

Eligibility Criteria

Eligible publications included original clinical investigations, randomized controlled trials, multicenter observational studies, systematic reviews, meta-analyses, prognostic model studies, and international consensus recommendations directly related to the diagnosis, selection, treatment, or prognosis of colorectal peritoneal metastases.

Priority was assigned to studies involving adult patients with colorectal malignancies and clearly described peritoneal involvement. Publications examining mixed peritoneal malignancy populations were considered when they provided relevant information about intraperitoneal treatment techniques, clinical implementation, or regional institutional experience.

Publications without sufficient methodological information, studies unrelated to colorectal peritoneal disease, and reports lacking meaningful clinical or oncological relevance were not prioritized. Experimental and early-phase investigations were considered separately from established clinical evidence to avoid presenting preliminary findings as definitive therapeutic recommendations.

Evidence Extraction and Critical Appraisal

The proposed analytical framework used a standardized evidence-extraction structure comprising publication year, study design, geographic setting, population characteristics, intervention, comparison group, principal outcomes, and methodological limitations.

Randomized clinical trials were prioritized when evaluating comparative treatment effectiveness, while systematic reviews and meta-analyses were used to examine the consistency of prognostic associations. Observational studies contributed information concerning surgical feasibility, long-term outcomes, and real-world treatment variability. Consensus documents were interpreted as clinical recommendations rather than independent demonstrations of treatment efficacy.

Critical appraisal focused on patient selection, potential confounding, study population heterogeneity, treatment protocol differences, outcome definitions, and applicability to contemporary multidisciplinary practice. Particular attention was directed toward distinguishing the oncological contribution of complete cytoreduction from the incremental effects of intraperitoneal chemotherapy.

Evidence Synthesis

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The evidence was organized into thematic categories corresponding to surgical eligibility, disease burden and prognostic indicators, completeness of cytoreduction, HIPEC regimens, systemic therapy, emerging intraperitoneal approaches, and oncological outcomes.

A qualitative comparative synthesis was chosen to identify convergent findings, conflicting results, limitations in the available evidence, and clinically relevant research gaps. No pooled effect estimates or new statistical comparisons were planned because the study was designed as a narrative rather than a quantitative systematic review.

The analysis additionally incorporated published Latin American experience to contextualize international recommendations within healthcare systems characterized by differences in specialized surgical availability, institutional resources, and access to multidisciplinary cancer care.

Reproducibility and Methodological Considerations

To support reproducibility, the methodological framework specifies the research questions, search terminology, eligibility principles, evidence-extraction variables, and analytical categories. Future investigators may replicate or update the review using the stated search strategy and standardized extraction structure.

Because this is a narrative review, its conclusions depend on the completeness, quality, and comparability of the published literature. The approach does not provide the exhaustive study identification or formal risk-of-bias assessment expected of a systematic review. These limitations are considered when interpreting the strength of evidence and formulating clinical conclusions.

The study relies exclusively on previously published research and does not involve direct patient contact, individual medical records, or experimental therapeutic interventions.

PHASES OF DEVELOPMENT

Identification and Delimitation of the Research Problem

The initial phase focused on defining the principal challenges associated with the management of CRPM. These included the heterogeneous distribution of peritoneal disease, difficulties in determining surgical eligibility, uncertainties surrounding the additional benefit of hyperthermic intraperitoneal chemotherapy (HIPEC), and substantial variability in reported oncological outcomes.

The research problem was delimited to three interconnected areas: selection of candidates for cytoreductive surgery (CRS), evaluation of intraperitoneal therapeutic strategies, and identification of clinical and biological factors influencing survival and recurrence.

Particular attention was given to the controversy generated by the PRODIGE 7 randomized trial, which demonstrated no significant overall survival improvement following the addition of the investigated oxaliplatin-based HIPEC regimen to CRS. This finding provided a foundation for examining whether favorable oncological outcomes depend predominantly on complete tumor removal, the characteristics of selected patients, or additional locoregional treatment [2], [3].

Formulation of Research Questions and Working Hypotheses

Following identification of the clinical problem, research questions were structured to examine relationships between patient characteristics, therapeutic interventions, and oncological outcomes.

The principal working hypothesis proposed that favorable outcomes following CRS are more consistently associated with complete macroscopic cytoreduction, limited peritoneal disease burden, and appropriate biological selection than with the routine addition of a particular intraperitoneal chemotherapy regimen.

A complementary hypothesis proposed that the therapeutic contribution of HIPEC may vary according to chemotherapeutic agent, administration protocol, tumor biology, and clinical context. These hypotheses were treated as interpretative propositions for evaluating published evidence rather than as assumptions requiring confirmation.

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The conceptual foundation was supported by previous investigations examining surgical completeness, prognostic factors, and the comparative effectiveness of intraperitoneal treatments [3], [9]–[11], [13].

Identification and Organization of Scientific Evidence

The bibliographic phase was structured around the search concepts and eligibility criteria described in the methodology. The reference framework incorporated foundational randomized clinical trials, multicenter observational investigations, systematic reviews, prognostic studies, and international consensus recommendations.

Relevant publications were organized according to study design, intervention, study population, and principal outcomes. Foundational trials were distinguished from contemporary investigations to account for differences in systemic chemotherapy, surgical techniques, and evolving standards of oncological care.

A separate analytical category was established for Latin American publications, permitting consideration of regional institutional experience and the applicability of international recommendations to healthcare systems with different resource availability [4]–[8], [19].

Critical Evaluation of Patient Selection Criteria

This phase addressed the clinical and prognostic variables used to identify potential candidates for CRS. The Peritoneal Cancer Index, anatomical distribution of metastatic deposits, completeness of cytoreduction, patient performance status, and relevant histopathological characteristics were examined as complementary selection parameters.

Evidence concerning these variables was compared to identify which characteristics showed consistent associations with survival and which remained subject to uncertainty. Particular attention was directed toward distinguishing potentially resectable disease from anatomically extensive involvement that could prevent complete cytoreduction or require functionally unacceptable resections.

Molecular prognostic factors were incorporated as an additional dimension, recognizing the growing relevance of RAS/RAF alterations and microsatellite instability while acknowledging the limited validation of molecular markers specifically for surgical eligibility [10]–[14].

Comparative Assessment of Therapeutic Strategies

The therapeutic evaluation phase examined CRS, HIPEC, perioperative systemic chemotherapy, and emerging intraperitoneal interventions.

Randomized evidence was prioritized when assessing treatment effectiveness. The historical survival findings from combined CRS-HIPEC studies were considered alongside the results of PRODIGE 7, with attention to differences in comparison groups, chemotherapy protocols, and clinical treatment eras.

The analysis distinguished therapeutic HIPEC for established metastases from prophylactic intraperitoneal interventions, considering the findings of PROPHYLOCHIP-PRODIGE 15 and COLOPEC. Studies investigating pressurized intraperitoneal aerosol chemotherapy were evaluated separately because their preliminary designs and populations limit direct comparison with established surgical treatment [3]–[8], [16]–[18].

Integration of Oncological Outcomes and Regional Evidence

The subsequent phase concentrated on identifying patterns across reported clinical outcomes, including overall survival, disease recurrence, postoperative complications, and treatment-related mortality.

Outcome interpretation considered differences in baseline tumor burden, completeness of cytoreduction, systemic therapy exposure, and institutional experience. This approach was intended to avoid attributing survival differences exclusively to treatment modality when underlying patient selection could substantially influence observed results.

Published Latin American experience was incorporated to contextualize the implementation of CRS and HIPEC within regional oncology practice. Findings from the Latin American Registry of Peritoneal Diseases were considered

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

particularly relevant to understanding collaborative development, treatment heterogeneity, and the need for standardized reporting across participating institutions [9], [15], [19].

Synthesis, Interpretation, and Identification of Research Gaps

The final phase involved integrating the principal findings into an evidence-based interpretation of contemporary CRPM management.

The synthesis was structured to distinguish relatively established principles, such as the importance of complete cytoreduction and careful patient selection, from unresolved questions concerning optimal HIPEC regimens, perioperative chemotherapy sequencing, molecularly guided treatment, and the long-term effectiveness of emerging intraperitoneal approaches.

Methodological limitations, including differences in study design, selection bias, heterogeneous treatment protocols, and restricted geographical representation, were considered when assessing the generalizability of findings.

This phase also established the conceptual basis for identifying future research priorities, particularly prospective comparative investigations, improved prognostic models, standardized oncological endpoints, and greater participation by Latin American institutions in international collaborative studies [1], [2], [14], [20].

RESULTS AND DISCUSSION

Figure 1.
Overall Survival Following Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy in Colorectal Peritoneal Metastases

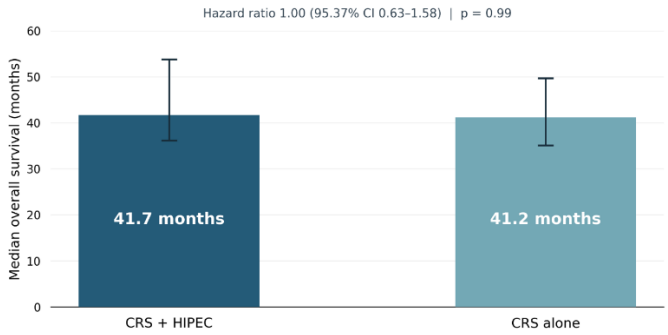

Figure 1 presents the comparative median overall survival outcomes reported in the PRODIGE 7 randomized phase III trial, which evaluated cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) against CRS alone in patients with colorectal peritoneal metastases. The study included 265 patients treated at 17 specialized French cancer centers, with 133 participants assigned to CRS plus HIPEC and 132 assigned to CRS alone. Randomization followed complete or near-complete macroscopic resection of peritoneal disease, permitting an assessment of the additional contribution of intraperitoneal chemotherapy within a population selected for surgical treatment [3].

Following a median observation period of 63.8 months, the median overall survival was 41.7 months (95% confidence interval [CI], 36.2–53.8) among patients receiving CRS plus HIPEC, compared with 41.2 months (95% CI, 35.1–49.7) among those undergoing CRS alone. The absolute difference between treatment groups was 0.5 months, corresponding to approximately 15 days. Although the combined-treatment group demonstrated a numerically higher median survival, the difference was minimal relative to the overall duration of survival reported in both study populations [3].

The comparison produced a hazard ratio for overall mortality of 1.00 (95.37% CI, 0.63–1.58), with a stratified log-rank p-value of 0.99. These findings indicated no statistically significant difference in overall survival between the randomized treatment groups. The confidence interval surrounding the hazard ratio also demonstrated uncertainty regarding the precise magnitude of the treatment effect, although the observed point estimate did not favor either therapeutic approach [3].

The relatively similar median survival values were accompanied by substantial overlap in their reported confidence intervals. The CRS plus HIPEC group demonstrated a confidence interval extending from 36.2 to 53.8 months, whereas the CRS-alone group presented an interval from 35.1 to 49.7 months. The graphical representation illustrates these

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Review International Science Journal

overlapping estimates without implying that comparison of the median confidence intervals alone constitutes the formal statistical test of treatment efficacy. The reported hazard ratio and log-rank analysis provide the principal inferential comparison between the randomized groups [3].

Regarding surgical completeness, complete macroscopic resection was achieved in 119 of 133 patients (89%) assigned to CRS plus HIPEC and 121 of 132 patients (92%) assigned to CRS alone. These proportions indicate that both groups consisted predominantly of patients in whom visible peritoneal disease had been completely removed. Therefore, the survival comparison reflects the addition of the investigated HIPEC protocol to extensive cytoreductive surgery rather than a comparison between surgical and nonsurgical management [3].

The trial also reported overall survival estimates at five years of approximately 39.4% in the CRS plus HIPEC group and 36.7% in the CRS-alone group. Although these percentages showed a numerical difference, the principal survival analysis did not identify a statistically significant advantage associated with the addition of HIPEC. The median survival findings and longer-term survival estimates were therefore broadly consistent in demonstrating similar overall survival outcomes between the two randomized strategies [3].

These results specifically correspond to the oxaliplatin-based HIPEC regimen evaluated in PRODIGE 7 and should be interpreted within the characteristics of its selected surgical population, treatment protocol, and follow-up period. Figure 1 summarizes the published median overall survival estimates and their uncertainty without extrapolating the findings to other chemotherapy agents, perfusion protocols, or patient populations not directly evaluated in the trial [3].

Figure 2.

Severe Postoperative Complications Following Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy

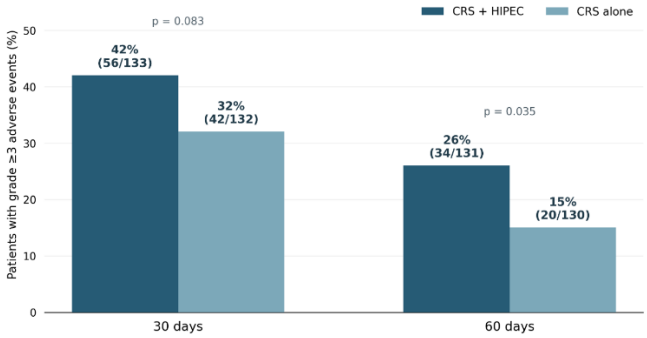

Figure 2 illustrates the frequency of severe postoperative adverse events among patients undergoing cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC), based on the safety outcomes reported in the PRODIGE 7 randomized phase III trial. The comparison includes adverse events classified as grade 3 or higher at postoperative assessments conducted at 30 and 60 days, providing quantitative information regarding the short-term morbidity associated with both therapeutic strategies [3].

At the 30-day assessment, severe adverse events were documented in 56 of 133 patients (42%) assigned to CRS plus HIPEC, compared with 42 of 132 patients (32%) treated with CRS alone. This corresponded to an absolute difference of approximately 10 percentage points between groups. Although the observed frequency was numerically higher following the combined procedure, the difference did not meet the conventional threshold for statistical significance ($p = 0.083$). These findings demonstrate a substantial burden of early postoperative morbidity in both treatment groups, consistent with the complexity of extensive peritoneal surgery [3].

At 60 days, grade 3 or higher adverse events were reported in 34 of 131 evaluable patients (26%) in the CRS plus HIPEC group and 20 of 130 patients (15%) in the CRS-alone group. The absolute difference was approximately 11 percentage points, with a statistically significant between-group comparison ($p = 0.035$). Therefore, the later postoperative assessment demonstrated a greater frequency of severe adverse events among patients receiving the combined surgical and intraperitoneal intervention [3].

An important methodological consideration concerns the interpretation of the two postoperative assessment periods. The reported percentages describe adverse events assessed at their respective time points and should not be interpreted as cumulative complication rates or as evidence that the incidence of complications declined from 30 to 60 days. The 60-day analysis included patients who had also experienced adverse events at the earlier assessment, and the denominators differed slightly between the two observation periods. Consequently, the results represent separate reported safety assessments rather than mutually exclusive groups of postoperative complications [3].

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

Regarding the characteristics of postoperative morbidity, digestive fistulas and intra-abdominal abscesses were among the complications documented in the original investigation. Digestive fistulas were reported in approximately 11% of patients receiving CRS plus HIPEC and 7% of those undergoing CRS alone, whereas intra-abdominal abscesses occurred in approximately 5% and 3%, respectively. These findings provide additional descriptive information regarding the types of abdominal complications observed during postoperative recovery [3].

Treatment-related mortality was also reported during follow-up. Within the first 30 postoperative days, two deaths occurred in each treatment group, corresponding to approximately 2% per group. Subsequent mortality assessments identified two additional treatment-related deaths in the combined-treatment group and one additional death in the surgery-alone group by the 60-day observation period. These outcomes were reported separately from the overall frequency of severe adverse events and were not included as additional categories in the graphical comparison [3].

The safety findings can also be considered alongside the survival outcomes presented in Figure 1. Whereas the principal survival analysis demonstrated similar median overall survival between treatment groups, the postoperative assessment identified a statistically significant difference in severe adverse events at 60 days. These are distinct clinical endpoints, and their comparative findings should be interpreted according to the original trial definitions rather than combined into a single measure of therapeutic effectiveness [3].

Overall, the figure provides a descriptive comparison of severe postoperative morbidity associated with CRS alone and CRS combined with the specific oxaliplatin-based HIPEC regimen investigated in PRODIGE 7. The results document numerically higher adverse-event frequencies in the combined-treatment group at both postoperative assessments, with statistical significance observed at 60 days. The available findings are restricted to the study population, treatment protocols, and safety definitions employed in the original randomized trial [3].

Figure 3.

Prognostic Factors Associated With Overall Survival After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

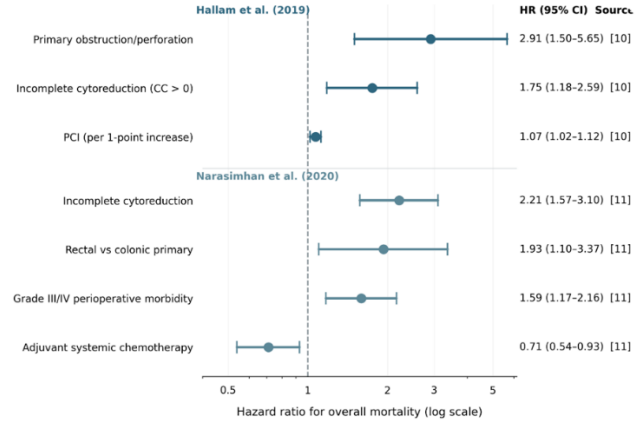

Figure 3 summarizes the association between selected clinical, pathological, and therapeutic factors and overall survival among patients undergoing cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases. The graphical representation incorporates pooled hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) from two previously published systematic reviews and meta-analyses. Hallam et al. included 24 studies involving 3,128 patients, whereas Narasimhan et al. identified 33 eligible studies, of which 25 contributed to their quantitative synthesis. The estimates are presented separately to preserve the methodological characteristics of each investigation [10], [11].

In the meta-analysis conducted by Hallam et al., obstruction or perforation of the primary colorectal tumor was associated with an increased hazard of mortality following CRS and HIPEC (HR 2.91; 95% CI, 1.50–5.65). This represented the largest point estimate among the prognostic associations selected from that investigation. The relatively wide confidence interval reflected uncertainty in the magnitude of the association, although its lower boundary remained above the reference value of 1.0. The result identified primary tumor obstruction or perforation as an adverse prognostic characteristic within the analyzed populations [10].

Completeness of cytoreduction demonstrated a consistent association with overall survival across both meta-analyses. Hallam et al. reported that a completeness of cytoreduction score greater than zero was associated with an increased mortality hazard (HR 1.75; 95% CI, 1.18–2.59). Similarly, Narasimhan et al. found that incomplete cytoreduction was associated with significantly worse survival (HR 2.21; 95% CI, 1.57–3.10). Although these estimates differ in magnitude, both indicate an adverse association between residual peritoneal tumor and long-term survival. The

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

definitions, contributing studies, and statistical models were not identical, and the estimates should therefore be interpreted independently rather than as interchangeable measurements [10], [11].

The extent of peritoneal dissemination, quantified using the Peritoneal Cancer Index (PCI), was another relevant prognostic variable. Hallam et al. reported an HR of 1.07 (95% CI, 1.02–1.12) for each one-point increase in PCI. This finding corresponds to a relative increase of approximately 7% in the estimated mortality hazard for each additional PCI point under the statistical model employed. The association is expressed on a continuous scale and is not directly equivalent to the binary comparisons used for other variables in Figure 3. Consequently, its proximity to the reference line should not be interpreted as indicating limited prognostic relevance [10].

Narasimhan et al. independently confirmed the adverse association between increasing PCI and survival, reporting an HR of 1.10 (95% CI, 1.05–1.15) per additional PCI point. Their analysis included eight studies involving 1,279 patients for this variable. Substantial statistical heterogeneity was reported (I^2 = 78%), indicating variation across the contributing investigations. Although this additional estimate is not included as a separate point in the figure, it provides complementary evidence regarding the relationship between peritoneal disease extent and mortality [11].

The anatomical origin of the primary malignancy was also associated with differences in survival. In the meta-analysis by Narasimhan et al., patients with a rectal primary tumor demonstrated an increased mortality hazard compared with patients whose primary tumor originated in the colon (HR 1.93; 95% CI, 1.10–3.37). This analysis included three studies involving 254 patients and showed no detected statistical heterogeneity (I^2 = 0%). The confidence interval remained above unity, indicating a statistically significant association within the analyzed population [11].

Postoperative morbidity constituted another prognostic factor. Narasimhan et al. reported that grade III or IV perioperative complications were associated with worse overall survival (HR 1.59; 95% CI, 1.17–2.16). Four studies involving 717 patients contributed to this comparison, with low statistical heterogeneity (I^2 = 18%). The result demonstrates an association between severe perioperative morbidity and subsequent mortality, although the observational nature of the contributing evidence limits causal interpretation [11].

Adjuvant systemic chemotherapy was the only selected variable in Figure 3 associated with a pooled hazard ratio below 1.0. Narasimhan et al. reported an HR of 0.71 (95% CI, 0.54–0.93), based on six studies involving 1,372 patients. This estimate corresponded to an approximately 29% lower mortality hazard among patients receiving adjuvant systemic chemotherapy in the contributing observational comparisons. Moderate heterogeneity was observed (I^2 = 43%). The finding represents a reported association rather than definitive evidence of a causal survival benefit [11].

The distribution of hazard ratios in Figure 3 illustrates differences in both the magnitude and precision of the selected prognostic associations. Obstruction or perforation of the primary tumor, incomplete cytoreduction, rectal tumor origin, and severe perioperative morbidity were associated with hazard ratios above unity. Increasing PCI also demonstrated an adverse association when assessed as a continuous variable, whereas adjuvant systemic chemotherapy was associated with a hazard ratio below unity. All selected confidence intervals excluded 1.0, although their widths varied across comparisons [10], [11].

Figure 4.
Clinical Outcomes of Investigational Intraperitoneal Therapies in Unresectable Colorectal Peritoneal Metastases

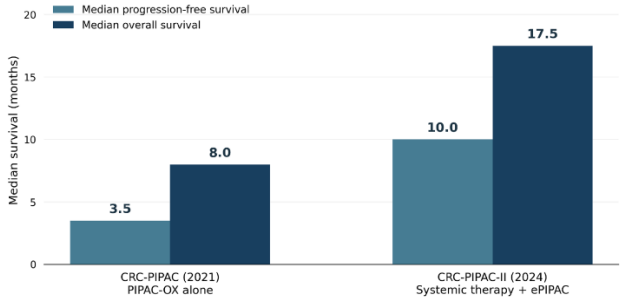

Figure 4 presents the progression-free survival (PFS) and overall survival (OS) outcomes reported in two prospective phase II clinical trials investigating pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with unresectable colorectal peritoneal metastases. The studies evaluated different therapeutic approaches: CRC-PIPAC examined oxaliplatin-based PIPAC as a palliative monotherapy, whereas CRC-PIPAC-II investigated the combination of first-line systemic chemotherapy with alternating electrostatic PIPAC (ePIPAC). Both trials enrolled 20 patients, providing descriptive evidence regarding treatment feasibility, antitumor activity, and survival in distinct clinical populations [16], [17].

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

In the CRC-PIPAC trial conducted by Rovers et al., 20 patients with unresectable colorectal peritoneal metastases underwent a total of 59 PIPAC procedures. The median number of procedures per patient was three, with a range of one to six. Oxaliplatin was administered intraperitoneally at a dose of 92 mg/m², with treatment intervals of approximately six weeks. The study permitted enrollment at different stages of palliative treatment, thereby including patients with variable prior exposure to systemic chemotherapy [16].

The reported median progression-free survival was 3.5 months, with an interquartile range (IQR) of 2.5–5.7 months. Median overall survival reached 8.0 months (IQR, 6.3–12.6 months). These outcomes describe the observed survival distribution within the study population following PIPAC monotherapy. The interquartile ranges represent the dispersion of individual survival observations and should not be interpreted as confidence intervals around the estimated medians [16].

The investigators additionally evaluated tumor response using several assessment methods. Radiological response was absent, with a reported response rate of 0%. In contrast, biochemical response was observed in 50% of evaluable patients, while pathological and ascites responses were each reported in 56% of their respective assessable populations. These findings demonstrate variation in observed treatment response according to the assessment method employed, with microscopic and biochemical changes not necessarily accompanied by measurable radiological tumor regression [16].

Regarding treatment-related morbidity, major adverse events were reported in three of the 20 patients (15%), occurring after five of the 59 procedures (8%). The documented events included abdominal pain, intraperitoneal hemorrhage, iatrogenic pneumothorax, and transient liver toxicity. One possibly treatment-related death, associated with sepsis of unknown origin, was also reported. Minor adverse events occurred in all patients, affecting 57 of the 59 procedures (97%). The median hospital stay was one day, with a range of zero to three days [16].

The subsequent CRC-PIPAC-II trial, conducted by Rauwerdink et al., evaluated a bidirectional therapeutic strategy combining first-line systemic chemotherapy with oxaliplatin-based electrostatic PIPAC. Patients received systemic treatment using CAPOX, FOLFOX, FOLFIRI, or FOLFOXIRI regimens combined with bevacizumab, alternating with intraperitoneal administration of oxaliplatin-based ePIPAC. Intravenous leucovorin and fluorouracil were also incorporated into the intraperitoneal treatment phase. This protocol therefore differed substantially from the monotherapy approach evaluated in CRC-PIPAC [17].

The study enrolled 20 chemotherapy-naïve patients, who completed a total of 52 treatment cycles. Median progression-free survival was 10.0 months (95% CI, 8.0–13.0 months), while median overall survival reached 17.5 months (95% CI, 13.0 months to not reached). These values were numerically higher than those reported in the preceding monotherapy trial; however, the investigations differed in previous treatment exposure, therapeutic regimen, patient selection, and treatment sequence. Consequently, the observed survival differences cannot be interpreted as direct estimates of comparative treatment effectiveness [16], [17].

Assessment of antitumor activity in CRC-PIPAC-II demonstrated a radiological response rate of 0%, a pathological response rate of 88%, a cytological response rate of 38%, and a biochemical response rate of 31%. Although radiological responses were not observed, pathological changes were documented in a substantial proportion of evaluable patients. Additionally, one patient underwent subsequent surgery with curative intent. These findings describe the heterogeneous response patterns reported following combined systemic and intraperitoneal treatment [17].

Major treatment-related adverse events occurred in seven of the 20 patients (35%), comprising 15 events overall. Of these events, five were attributed to systemic therapy, five to ePIPAC, and five were classified as biochemical adverse events. No treatment-related deaths were reported. Minor adverse events occurred in all patients, most commonly abdominal pain, nausea, and peripheral sensory neuropathy. The different treatment exposures and adverse-event classifications between the two studies limit direct comparison of their safety percentages [16], [17].

The graphical representation highlights the difference in reported survival outcomes between the two investigational treatment protocols. CRC-PIPAC demonstrated median PFS and OS values of 3.5 and 8.0 months, respectively, whereas CRC-PIPAC-II reported corresponding values of 10.0 and 17.5 months. These differences are presented descriptively, without calculating comparative hazard ratios, statistical significance, or treatment-attributable survival benefits, because neither trial included a concurrent control group [16], [17].

Both studies reported the absence of objective radiological tumor responses despite documenting pathological or other forms of treatment response. However, the proportion of pathological responses differed between investigations, reaching 56% in CRC-PIPAC and 88% in CRC-PIPAC-II. These values originated from separate study populations and response-assessment procedures, and their comparison is therefore descriptive rather than inferential [16], [17].

DISCUSSION

The findings of this narrative review highlight the complexity of contemporary management of colorectal peritoneal metastases (CRPM), particularly regarding surgical candidate selection, the therapeutic contribution of intraperitoneal

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

chemotherapy, and long-term oncological outcomes. The available evidence suggests that treatment effectiveness depends on the interaction between peritoneal disease burden, anatomical resectability, tumor biology, patient characteristics, and postoperative morbidity. Although cytoreductive surgery (CRS) represents an important therapeutic option for carefully selected patients, considerable uncertainty remains regarding the additional benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) and the optimal integration of systemic treatments [1]–[3], [10], [11].

Cytoreductive Surgery and Patient Selection

One of the most consistent findings across the reviewed literature is the association between complete macroscopic cytoreduction and improved overall survival. The prognostic analyses presented in Figure 3 demonstrated that incomplete cytoreduction was associated with increased mortality, with hazard ratios of 1.75 and 2.21 reported by Hallam et al. and Narasimhan et al., respectively. Although these estimates originated from different populations and analytical approaches, both demonstrated an unfavorable association between residual macroscopic disease and long-term survival [10], [11].

Nevertheless, these findings require careful interpretation because patients eligible for complete cytoreduction frequently present with more favorable anatomical characteristics, lower tumor burden, and better functional status. Consequently, the survival differences observed in nonrandomized investigations may reflect both the effectiveness of surgical treatment and the prognostic characteristics of selected patients. This distinction is particularly relevant when comparing surgical outcomes with those of patients receiving systemic therapy alone, since the latter population may include individuals with extensive or technically unresectable disease [9], [12], [15].

The Peritoneal Cancer Index (PCI) remains a fundamental instrument for evaluating disease extent and estimating surgical feasibility. Increasing PCI values have been associated with unfavorable survival outcomes, although their clinical significance depends on the anatomical distribution of metastatic deposits. Extensive small bowel involvement, mesenteric infiltration, and the possibility of preserving adequate gastrointestinal function may influence resectability independently of the total PCI score. Therefore, surgical eligibility should be established through comprehensive multidisciplinary assessment rather than reliance on a single numerical threshold [1], [10], [11].

Therapeutic Relevance and Controversies Surrounding HIPEC

The results of the PRODIGE 7 randomized phase III trial constitute one of the most important developments in the contemporary evaluation of HIPEC. As demonstrated in Figure 1, median overall survival was 41.7 months among patients receiving CRS combined with oxaliplatin-based HIPEC and 41.2 months among those undergoing CRS alone. The absence of a statistically significant difference challenged the assumption that intraperitoneal chemotherapy necessarily improves survival following complete or near-complete cytoreduction [3].

These findings differ from the historical interpretation of earlier studies, particularly the randomized investigation conducted by Verwaal et al., which demonstrated improved survival with combined CRS-HIPEC compared with conventional treatment available at that time. However, the earlier trial compared a comprehensive locoregional treatment strategy against systemic chemotherapy and palliative surgery, whereas PRODIGE 7 specifically evaluated the incremental contribution of HIPEC after extensive surgical cytoreduction. Differences in study design, systemic chemotherapy regimens, surgical selection criteria, and treatment periods therefore limit direct comparison of their findings [3]–[5].

Importantly, the results of PRODIGE 7 should not be generalized to all intraperitoneal chemotherapy protocols. The trial evaluated a specific short-duration, high-dose oxaliplatin regimen, while alternative approaches involving mitomycin C differ in pharmacological characteristics and administration protocols. International consensus recommendations have consequently distinguished the lack of demonstrated benefit from the investigated oxaliplatin regimen from the unresolved effectiveness of other HIPEC strategies. Nevertheless, the evidence supporting alternative regimens remains insufficient to establish a universal survival advantage [2], [3], [18].

Postoperative Morbidity and Clinical Outcomes

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

The postoperative complication rates presented in Figure 2 emphasize the importance of considering treatment-related morbidity alongside potential oncological benefits. In PRODIGE 7, severe postoperative adverse events at 60 days occurred in 26% of patients receiving CRS plus HIPEC compared with 15% undergoing CRS alone. This statistically significant difference demonstrates that the addition of the investigated intraperitoneal chemotherapy protocol was associated with increased severe morbidity during postoperative recovery [3].

The prognostic significance of postoperative complications is further supported by the meta-analysis conducted by Narasimhan et al., which identified an association between severe perioperative morbidity and increased mortality. These findings suggest that postoperative recovery represents an important component of long-term oncological outcomes, particularly when complications delay systemic treatment, compromise nutritional status, or reduce functional capacity [11].

However, postoperative morbidity is influenced by numerous factors, including the extent of peritoneal disease, duration of surgery, number of visceral resections, previous treatments, and institutional experience. Consequently, complication rates reported by specialized centers should not automatically be extrapolated to all healthcare settings. Appropriate surgical training, perioperative optimization, and multidisciplinary postoperative care remain essential considerations when evaluating the safety of aggressive locoregional treatment [1], [9], [20].

Molecular Prognostic Factors and Personalized Treatment

Molecular characterization has progressively expanded the understanding of biological heterogeneity in colorectal peritoneal metastases. Alterations involving KRAS, NRAS, and BRAF, together with microsatellite instability status, may influence tumor progression, responsiveness to systemic therapies, and survival outcomes. The investigation conducted by Tonello et al. contributed evidence regarding the prognostic relevance of molecular alterations among patients undergoing CRS and HIPEC [13].

Nevertheless, molecular characteristics should not currently be interpreted as independent determinants of surgical eligibility. Although certain alterations may be associated with unfavorable prognosis, their clinical relevance depends on the interaction between tumor biology, anatomical disease extent, and available therapeutic options. Integrating molecular information into validated prognostic models may improve individualized treatment selection, but additional prospective evidence is required before such approaches can be routinely implemented [12]–[14].

Emerging investigations involving colorectal cancer consensus molecular subtypes have also suggested potential differences in sensitivity to intraperitoneal chemotherapeutic agents. These findings introduce the possibility of future molecularly guided intraperitoneal treatment strategies. However, experimental drug sensitivity does not necessarily translate into improved clinical survival, and the available evidence remains insufficient to recommend specific HIPEC regimens according to molecular subtype [14].

Emerging Intraperitoneal Therapies and Systemic Chemotherapy

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) represents an investigational strategy for patients with unresectable colorectal peritoneal metastases. The findings presented in Figure 4 demonstrated differences in reported survival between CRC-PIPAC and CRC-PIPAC-II, with median overall survival values of 8.0 and 17.5 months, respectively. However, these investigations involved different treatment protocols, prior treatment exposures, and patient populations, preventing direct conclusions regarding comparative therapeutic effectiveness [16], [17].

The absence of objective radiological responses despite the identification of pathological responses in both investigations illustrates the difficulties associated with assessing peritoneal disease using conventional imaging criteria. Small tumor deposits, diffuse peritoneal involvement, and changes in tumor cellularity may not be adequately represented by radiological measurements. Nevertheless, pathological response should not be assumed to predict improved overall survival without further validation [16], [17].

Systemic chemotherapy also remains an essential component of multidisciplinary treatment. The association between adjuvant systemic chemotherapy and reduced mortality reported in prognostic analyses supports continued investigation of combined therapeutic strategies. However, observational associations may be influenced by differences in postoperative recovery, functional status, and baseline disease characteristics. The randomized phase II

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

investigation conducted by Rovers et al. provided additional evidence regarding the feasibility of perioperative systemic treatment, although its definitive contribution to survival remains uncertain [8], [11].

The optimal sequencing of systemic chemotherapy and CRS therefore continues to represent an important research question. Neoadjuvant treatment may facilitate evaluation of tumor responsiveness and occult systemic disease, whereas postoperative chemotherapy may contribute to controlling residual microscopic disease. However, treatment-related toxicity, disease progression during chemotherapy, and postoperative recovery must be considered when determining individualized therapeutic strategies [8], [15].

International Evidence and Latin American Participation

International advances in peritoneal surface oncology have contributed to the development of specialized surgical programs, standardized assessment tools, and multidisciplinary treatment recommendations. Nevertheless, access to these interventions remains heterogeneous across healthcare systems, particularly where institutional resources, surgical expertise, and specialized oncological infrastructure are limited [1], [20].

The Latin American Registry of Peritoneal Diseases provides evidence of regional participation in the development of CRS-HIPEC programs. Although the registry includes several types of peritoneal malignancies, its findings demonstrate the establishment of specialized surgical activity and collaborative clinical experience across Latin American institutions. This regional contribution is relevant because the applicability of international recommendations may be influenced by differences in healthcare organization, treatment availability, and institutional resources [19].

However, the available Latin American evidence remains limited by differences in institutional reporting, patient selection, treatment protocols, and follow-up methods. Greater participation in prospective multicenter investigations could improve the regional representativeness of clinical evidence and facilitate comparisons with established international treatment programs. Standardized registries and collaborative research networks may also contribute to evaluating postoperative morbidity, survival, and quality of life under different healthcare conditions [1], [19], [20].

Methodological Limitations and Future Research Directions

Several methodological limitations should be considered when interpreting the findings of this review. First, the available evidence includes heterogeneous investigations ranging from randomized controlled trials to observational cohorts, systematic reviews, prognostic analyses, and early-phase clinical studies. These designs differ in their capacity to establish causal relationships and frequently involve distinct clinical populations [3], [9]–[11].

Second, differences in PCI distributions, completeness-of-cytoreduction definitions, systemic chemotherapy exposure, and HIPEC administration protocols complicate direct comparisons between studies. Consequently, numerical differences in survival should not automatically be interpreted as evidence of treatment superiority when the underlying populations and interventions are not equivalent [2], [3], [16], [17].

Third, selection bias remains particularly relevant in observational investigations of CRS. Patients undergoing complete cytoreduction frequently possess favorable clinical and anatomical characteristics, making it difficult to distinguish the effects of treatment from differences in baseline prognosis. Furthermore, the limited availability of standardized quality-of-life outcomes restricts comprehensive assessment of the relationship between survival benefits and treatment burden [9]–[12].

The narrative design of this review also imposes limitations because it does not incorporate an exhaustive systematic screening process, formal risk-of-bias assessment, or original quantitative meta-analysis. Accordingly, its conclusions should be interpreted as a critical synthesis of selected published evidence rather than definitive estimates of comparative treatment effectiveness.

Future research should prioritize prospective randomized investigations comparing standardized intraperitoneal chemotherapy protocols, validation of prognostic models integrating anatomical and molecular characteristics, and improved assessment of postoperative functional outcomes. Greater inclusion of Latin American institutions in

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

international research networks would also strengthen the applicability of future findings across diverse healthcare systems [1], [2], [14], [19].

Clinical Implications and Overall Interpretation

The collective evidence supports an individualized approach to colorectal peritoneal metastases in which surgical eligibility is determined through comprehensive assessment of tumor burden, anatomical resectability, biological characteristics, and patient condition. Complete macroscopic cytoreduction remains consistently associated with favorable survival outcomes, while the additional contribution of intraperitoneal chemotherapy depends on the specific treatment protocol and the strength of supporting clinical evidence [1]–[3], [10], [11].

The findings also demonstrate that therapeutic effectiveness should not be evaluated exclusively through overall survival. Postoperative morbidity, disease recurrence, functional recovery, and quality of life constitute complementary outcomes that may influence the overall clinical value of treatment. This consideration is particularly important when evaluating extensive surgical interventions or emerging therapies supported primarily by preliminary evidence [3], [16], [17].

Ultimately, progress in the management of colorectal peritoneal metastases will depend on improving patient selection, refining surgical techniques, establishing the comparative effectiveness of intraperitoneal treatments, and expanding access to specialized multidisciplinary care. Integrating international evidence with regional clinical experience, particularly from Latin America, may contribute to more consistent therapeutic decisions and improved oncological outcomes [1], [19], [20].

CONCLUSION

The management of colorectal peritoneal metastases represents a complex challenge in contemporary surgical oncology, requiring the integration of clinical, anatomical, molecular, and therapeutic factors to achieve favorable oncological outcomes. The evidence examined in this review supports the importance of individualized patient selection and complete macroscopic cytoreduction as central determinants of long-term survival. Nevertheless, the effectiveness of aggressive surgical management remains closely associated with disease burden, anatomical resectability, tumor biology, and the patient's physiological condition [1], [10], [11].

Cytoreductive surgery constitutes an important therapeutic option for carefully selected patients, particularly when complete removal of visible peritoneal disease is technically feasible. The Peritoneal Cancer Index, completeness of cytoreduction, histopathological characteristics, and molecular alterations provide complementary information for prognostic assessment. However, no individual parameter adequately captures the biological and clinical heterogeneity of colorectal peritoneal metastases, reinforcing the need for comprehensive multidisciplinary evaluation [9]–[14].

The role of hyperthermic intraperitoneal chemotherapy remains controversial. The PRODIGE 7 trial demonstrated no significant overall survival improvement following the addition of the investigated oxaliplatin-based HIPEC regimen to cytoreductive surgery, while identifying an increased frequency of severe postoperative complications at 60 days. These findings emphasize the importance of distinguishing the established prognostic relevance of complete cytoreduction from the uncertain incremental benefit of particular intraperitoneal chemotherapy protocols. Alternative regimens, including mitomycin C-based approaches, require further investigation before definitive conclusions can be established [2], [3], [18].

Emerging intraperitoneal strategies, particularly pressurized intraperitoneal aerosol chemotherapy, have demonstrated feasibility and preliminary antitumor activity in patients with unresectable disease. However, the available phase II evidence does not establish a definitive survival advantage, and direct comparisons between different treatment protocols remain limited. Similarly, the optimal sequencing and duration of perioperative systemic chemotherapy require additional prospective evaluation [8], [16], [17].

From an international perspective, the development of specialized peritoneal surface oncology programs has contributed to advances in surgical management and multidisciplinary care. Latin American participation demonstrates growing regional experience, although disparities in institutional resources, treatment accessibility, and research

Issue 4, Year 2, Volume 1, No. 02, July-December 2026
E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

infrastructure remain important challenges. Expanding multicenter collaboration and standardized clinical registries may strengthen the generation of regionally representative evidence [1], [19], [20].

In conclusion, **the most consistent findings support careful patient selection, complete macroscopic cytoreduction, and individualized multidisciplinary management as fundamental components of treatment for colorectal peritoneal metastases**. Future investigations should prioritize the validation of integrated prognostic models, comparative evaluation of intraperitoneal therapeutic regimens, reduction of postoperative morbidity, and assessment of patient-centered outcomes. Advancing these priorities will be essential to refine therapeutic indications, improve oncological results, and promote more equitable access to specialized treatment across international healthcare settings.

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