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Perioperative systemic therapy for resectable colorectal peritoneal metastases: Sufficient evidence for its widespread use? A critical systematic review

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ABSTRACT

Background/Purpose: Despite its widespread use, no randomised studies have investigated the value of perioperative systemic therapy as adjunct to cytoreduction and HIPEC for colorectal peritoneal metastases. This systematic review evaluated the available evidence, which consists of non-randomised studies only.

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Methods: A systematic search identified studies that investigated the influence of neoadjuvant, adjuvant, or perioperative systemic therapy on overall survival (OS).
Results: The 11 included studies (n = 1708) were clinically heterogeneous and subject to selection bias. Studies on neoadjuvant systemic therapy revealed OS benefit (n = 3), no OS benefit (n = 1), and superiority of chemotherapy with bevacizumab vs. chemotherapy (n = 2). Studies on adjuvant systemic therapy showed no OS benefit (n = 3). Studies on perioperative systemic therapy demonstrated OS benefit (n = 1), and superiority of modern vs. conventional systemic therapy(n = 1).
Conclusion: Significant limitations of available evidence question the widespread use of perioperative systemic therapy in this setting, stress the need for randomised studies, and impede conclusions regarding optimal timing and regimens. Included studies may suggest a survival benefit of neoadjuvant systemic therapy.

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1. Introduction

The population-based survival of patients with colorectal cancer with peritoneal metastases (CRC-PM) has significantly improved during the last two decades, which has been at least partly attributed to the increased use of modern chemotherapy, targeted agents, and cytoreductive surgery with HIPEC (CRS/HIPEC) (Razenberg et al., 2016a,b). The intensification of systemic and surgical treatment has led to combined treatment strategies, with widespread use of perioperative systemic therapy, both neoadjuvant and adjuvant, in patients who undergo CRS/HIPEC for CRC-PM.In contrast to resectable colorectal liver metastases, no randomised studies have been performed on perioperative systemic therapy for resectable CRC-PM, leading to controversy regarding its efficacy, timing, and risks (Esquivel et al., 2007; Nordlinger et al., 2013). As a result, timing of systemic therapy between HIPEC centres varies from neoadjuvant to adjuvant, both, or nothing. These disparities may lead to a risk of undertreatment, overtreatment, and unnecessary health care costs, thereby underlining the importance of randomised studies on these increasingly combined and accepted treatment modalities (Baratti et al., 2016).However, in the absence of such studies, non-randomised studies should be evaluated to assess the quality of currently available evidence, provide future research directions, and identify potentially beneficial perioperative systemic treatment strategies. With these goals kept in mind, this study systematically reviewed the evidence regarding the influence of perioperative systemic therapy on overall survival (OS) and postoperative complications in patients who undergo CRS/HIPEC for CRC-PM.

2. Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. Two researchers (KR and GS) independently performed the study selection, data collection, and risk of bias assessment. In case of disagreement, a final decision was made in consensus between the two researchers.

2.1. Eligibility criteria

Studies were considered potentially eligible when they included patients who underwent CRS with intraperitoneal chemotherapy (IPC) for CRC-PM, and analysed the influence of neoadjuvant, adjuvant, or perioperative systemic therapy on OS or postoperative complications. Subsequently, studies were considered ineligible if detailed information on survival outcomes, postoperative complication rates, or systemic therapy regimens was lacking, or if outcomes were analysed in patients with peritoneal metastases from various primary tumours without providing subgroup analysis for CRC-PM. No restrictions were applied on language, publication date, and publication status.

2.2. Search

On 4 January 2017, PubMed/MEDLINE, EMBASE, and Cochrane were systematically searched without date restrictions by using relevant synonyms of 'colorectal cancer', 'peritoneal metastases', 'cytoreductive surgery', 'intraperitoneal chemotherapy', and 'systemic therapy' (Supplementary Table 1).

2.3. Study selection

Titles and abstracts were screened for potential eligibility according to the predefined eligibility criteria. In case of disagreement about potential eligibility, full text was examined. Subsequently, full texts of all potentially eligible manuscripts were screened for final eligibility. Reference lists of all potentially eligible manuscripts were searched to identify additional eligible manuscripts.

2.4. Data collection

Data collection was performed by using a standardised form that contained the following items: year of publication, study design, number of patients, years of patient inclusion, study setting, inclusion criteria, surgical procedures, (measurement of) extent of PM, completeness of cytoreduction, IPC timing, IPC technique, IPC drugs, number of patients who received (neo)adjuvant systemic therapy, (neo)adjuvant systemic therapy regimens, outcome assessment, overall survival, and grade III–V postoperative complications.Systemic therapy regimens were classified as 'single agent chemotherapy' if they consisted of a fluoropyrimidine ± leucovorin, as 'combination chemotherapy' if they consisted of single agent chemotherapy with oxaliplatin, irinotecan, or cisplatin, and as 'combination chemotherapy with targeted therapy' if they consisted of combination chemotherapy with targeted agents (e.g. bevacizumab, cetuximab). All other regimens were classified as 'other'. Timing of systemic therapy was classified as neoadjuvant, adjuvant, or perioperative if studies did not distinguish between neoadjuvant and adjuvant. Postoperative complications were graded according to Clavien-Dindo or the National Cancer Institute Common Terminology for Adverse Events (NCICTCAE) (Dindo et al., 2004; Trotti et al., 2003).

2.5. Risk of bias in individual studies

Methodological quality of included studies was assessed at individual study level by using the methodological index for non-randomised studies (Slim et al., 2003).

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