

## Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal metastases

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### Abstract

**AIM:** To systematically review the available evidence regarding cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) for colorectal peritoneal metastases (CPM).

**METHODS:** An electronic literature search was carried out to identify publications reporting oncological outcome data (overall survival and/or disease free survival and/or recurrence rates) following CRS and IPC for treatment of CPM. Studies reporting outcomes following

CRS and IPC for cancer subtypes other than colorectal were only included if data were reported independently for colorectal cancer-associated cases; in addition studies reporting outcomes for peritoneal carcinomatosis of appendiceal origin were excluded.

**RESULTS:** Twenty seven studies, published between 1999 and 2013 with a combined population of 2838 patients met the predefined inclusion criteria. Included studies comprised 21 case series, 5 case-control studies and 1 randomised controlled trial. Four studies provided comparative oncological outcome data for patients undergoing CRS in combination with IPC *vs* systemic chemotherapy alone. The primary indication for treatment was CPM in 96% of cases (2714/2838) and recurrent CPM (rCPM) in the remaining 4% (124/2838). In the majority of included studies (20/27) CRS was combined with hyperthermic intraperitoneal chemotherapy (HIPEC). In 3 studies HIPEC was used in combination with early post-operative intraperitoneal chemotherapy (EPIC), and 2 studies used EPIC only, following CRS. Two studies evaluated comparative outcomes with CRS + HIPEC *vs* CRS + EPIC for treatment of CPM. The delivery of IPC was performed using an "open" or "closed" abdomen approach in the included studies.

**CONCLUSION:** The available evidence presented in this review indicates that enhanced survival times can be achieved for CPM after combined treatment with CRS and IPC.

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**Key words:** Colorectal cancer; Peritoneal metastasis; Cytoreductive surgery; Intraperitoneal chemotherapy; Hyperthermic intraperitoneal chemotherapy

**Core tip:** Colorectal cancer peritoneal metastases (CPM) confer a dismal prognosis and traditional treatment involving systemic chemotherapy, with or without pallia-

tive surgery has poor outcomes. Cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy (IPC) is now advocated for selected patients with CPM. The present study provides a comprehensive summary of the available evidence relating to CRS in combination with IPC in the setting of CPM, focusing on techniques, oncological outcomes, and complications.

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## INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-associated mortality world-wide with over 1 million new cases diagnosed annually<sup>[1]</sup>. Disseminated disease represents the principal cause of mortality in CRC and a significant proportion of patients are found to have locally advanced or systemically disseminated disease at initial presentation. It is estimated that at the time of diagnosis 30%-40% have locally advanced disease (Stage II-III) and approximately 20% have distant metastases (Stage IV)<sup>[2,3]</sup>. Haematogenous spread to the liver is the most common route for distant-organ dissemination, followed by pulmonary metastases<sup>[4]</sup>. Historically, patients with stage IV disease have been offered supportive therapy only, with 5-year survival rarely exceeding 5%<sup>[5]</sup>. Over the past two decades the widespread use of newer chemotherapeutic agents such as irinotecan and oxaliplatin, as well as novel targeted therapies, have led to a significant improvement in progression-free and overall survival in stage IV CRC<sup>[6,7]</sup>. In parallel there has been sharp increase in the volume of surgical resections/ablative procedures being undertaken for stage IV disease, and curative intent hepatic and pulmonary metastasectomy are now routinely performed<sup>[8,9]</sup>.

Synchronous peritoneal carcinomatosis is identified at primary surgery in approximately 5%-10% of patients undergoing CRC resection<sup>[10-12]</sup>. Additionally up to 20%-50% of patients undergoing curative intent colorectal cancer resection can go on to develop disease recurrence limited to the peritoneal cavity<sup>[10]</sup>. In theory, the development of colorectal peritoneal disease starts with primary tumour rupture or invasion through the serosa, followed by seeding of free intra-peritoneal tumour cells<sup>[13]</sup>. The precise mechanistic principles that govern distribution within the peritoneal cavity are multifactorial and have been well described and referred to as “redistribution phenomena”<sup>[14,15]</sup>. Briefly, these factors include gravitational pooling of cancer-cell containing fluid in the pelvis, clockwise directional flow of peritoneal fluid in the abdominal cavity leading to sub-phrenic implanta-

tion<sup>[16]</sup>, and phagocytic activity of the greater and lesser omentum which leads to the formation of characteristic “omental cake” deposits<sup>[16-18]</sup>.

The presence of peritoneal disease in the context of CRC confers a dismal prognosis, and traditional treatment involving systemic chemotherapy, with or without palliative surgery (typically reserved for acute complications such as intestinal obstruction) is associated with a median survival of 5-7 mo<sup>[10-12]</sup>. Since the 1990s however, several pioneering groups around the world have sought to employ more radical strategies for the treatment of peritoneal surface malignancy. Cytoreductive surgery (CRS), popularised by Sugarbaker initially for relatively non-invasive tumours such as Pseudomyxoma Peritonei<sup>[19,20]</sup>, is now offered to selected patients at specialist units for what is best termed “Colorectal peritoneal metastases (CPM)”, analogous to the concept of resectable liver metastases<sup>[21]</sup>. The aim of CRS is to remove all macroscopic disease through peritonectomy and multi-visceral resections where required. The extensiveness of these approaches varies according to cancer volume and anatomical location; CPM involving visceral peritoneal surfaces requires organ resection at times<sup>[13,19]</sup>, while treatment of disease confined to the parietal peritoneum involves more limited regional peritoneal stripping<sup>[20]</sup>.

The combination of these surgical approaches with peri-operative intra-peritoneal chemotherapy (IPC) has been advocated in order to eradicate residual cancer cells after macroscopic cytoreduction<sup>[22]</sup>. The peritoneal route of chemotherapy is based on the peritoneal-plasma partition concept whereby a high concentration of the chemotherapy is in direct contact with cancerous cells with minimal systemic absorption and side effects. A variety of strategies have been proposed and investigated including hyperthermic intraperitoneal chemotherapy (HIPEC)<sup>[23,24]</sup> and early post-operative intraperitoneal chemotherapy (EPIC)<sup>[25]</sup>. The rationale for this combination in favour of systemic therapy alone stems from the understanding that reducing tumour burden represents a critical factor in achieving tumour response to chemotherapy<sup>[13]</sup>. This notion is supported by the findings of a Dutch randomized-controlled trial (RCT) which reported significantly improved survival outcomes with CRS and HIPEC compared with systemic chemotherapy alone for patients with CPM<sup>[26]</sup>. Despite these encouraging reports, the otherwise lack of level-1 evidence and concerns with respect to peri-operative morbidity, mortality, quality of life, and healthcare related costs, have polarised opinions regarding these aggressive multi-modality approaches, and the management of CPM remains controversial<sup>[21]</sup>.

To date there has been only one systematic review and meta-analysis of data regarding the utility of CRS and IPC in the context of CPM<sup>[27,28]</sup>.

The present study therefore aims to provide an up-to-date systematic review of the available literature regarding the use of CRS in combination with intra-peritoneal chemotherapy for treatment of CPM specifically. In particular, we focus on the current techniques, oncological

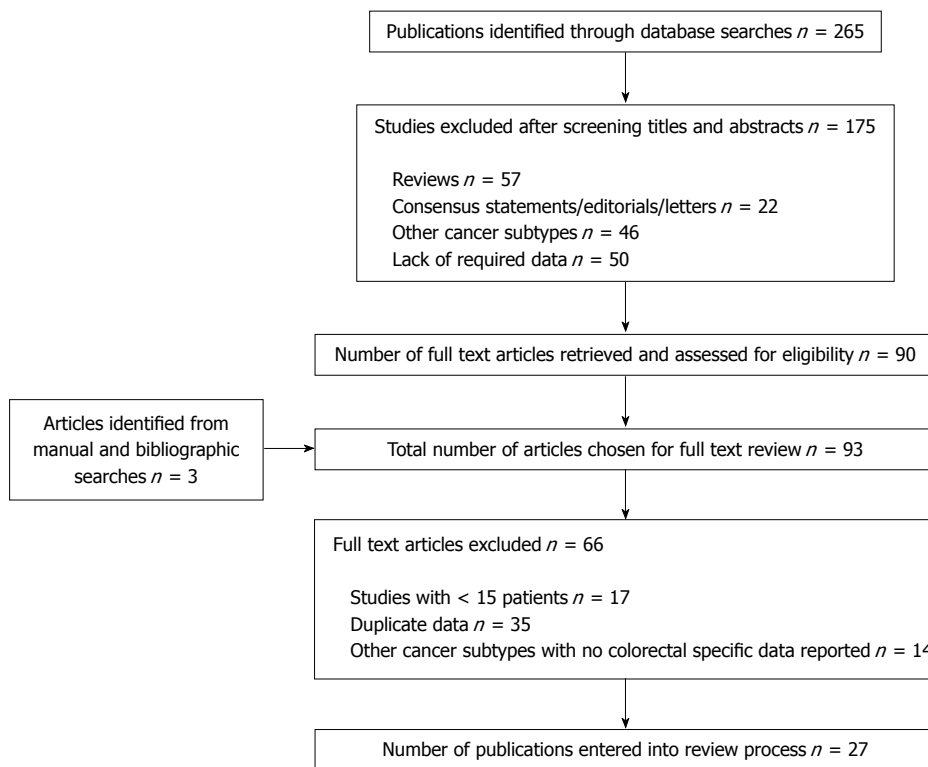


Figure 1 Modified preferred reporting items for systematic reviews and meta-analyses flow diagram outlining study selection strategy.

outcomes, and associated complications.

## MATERIALS AND METHODS

### Identification of studies

An electronic literature search was carried out using the following medical subject heading (MeSH) terms: “colorectal cancer”; “peritoneal”; “carcinomatosis”; “cytoreductive surgery”; “chemotherapy”; “intra-operative”; “intra-peritoneal”. The “related articles” function was used to broaden search output. All potentially eligible publications were obtained in full text and assessed for suitability. Text references were manually searched for identification of additional eligible studies.

### Study inclusion criteria and data extraction

Review methodology was conducted according to guidelines outlined in the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” framework<sup>[29]</sup>. Identified publications had to meet the following criteria to be included in the systematic review process: (1) English language; (2)  $\geq 15$  male/female adult patients ( $\geq 18$  years); and (3) histologically verified diagnosis of CPM receiving multi-modality treatment with CRS and IPC. Studies reporting outcomes following CRS and IPC for cancer subtypes other than colorectal were only included if survival outcome data were reported independently for CRC-associated cases; in addition studies reporting outcomes in patients undergoing treatment for peritoneal disease of appendiceal origin were excluded, as there is significant variation in the natural history and

prognosis of this sub-group of patients<sup>[28]</sup>; and (4) reporting oncological outcome data (survival and/or recurrence rates). Complication related data was also extracted where provided. Where multiple studies with potentially overlapping patient populations were identified, the most recent study was included. Figure 1 summarizes the review search strategy. Two reviewers (RM and AHM) derived the following data from eligible publications: author, location, year of publication and study time-frame, study type, population characteristics, primary or recurrent disease, stage of CPM [peritoneal cancer index (PCI)<sup>[30]</sup> or alternative scoring method for disease extent], chemotherapeutic regimen, details of previous treatment (chemotherapy/radiotherapy), length of follow-up, treatment associated morbidity and mortality, completeness of cytoreduction [completeness of cytoreduction (CCR) score<sup>[31]</sup> and/or R-classification where reported], oncological data (survival and/or recurrence rates). Studies that met inclusion criteria were evaluated based on methodological quality and validity using the Scottish Intercollegiate Guidelines Network (SIGN) framework<sup>[32]</sup>.

## RESULTS

### Literature search and description of studies

Initial literature searching identified 265 publications of potential relevance. From these 57 reviews and 118 irrelevant studies were excluded, leaving 90 articles retrieved in full text. Manual reference searches from these articles revealed an additional 3 potentially eligible publications, providing a total of 93 articles. Of these, 66

**Table 1 Summary of study design, treatment indications and treatment protocols for studies included in systematic review process n (%)**

Ref.	Time frame	n	Study design (evidence level)	Indication	Extent of CPM	Treatment summary	Technique	Intraperitoneal chemotherapeutic regimen
Portilla <i>et al.</i> <sup>[33]</sup>	1985-1996	18	Case series (3)	rCPM <sup>1</sup>	PCI < 12, 10/18 (60) PCI > 12, 8/18 (38)	CRS + EPIC	Closed technique	POD 1: MMC in 1 L 1.5% dextrose peritoneal dialysis solution (10-12.5 mg/m <sup>2</sup> ) POD 2-6: 5-FU in 1 L 1.5% dextrose peritoneal dialysis solution + 50 mEq sodium bicarbonate
Witkamp <i>et al.</i> <sup>[34]</sup>	1995-1997	29	Case series (3)	CPM <sup>2</sup>	-	CRS + HIPEC	Closed technique	MMC 35 mg/m <sup>2</sup> in 3-4 L of isotonic dialysis fluid at a temperature of 40 °C-41 °C for 90 min
Pilati <i>et al.</i> <sup>[35]</sup>	1995-2001	34	Case series (3)	CPM <sup>2</sup>	-	CRS + HIPEC	10/34 closed technique 14/34 open technique	MMC (3.3 mg/m <sup>2</sup> per liter) + cisplatin (25 mg/m <sup>2</sup> per liter) for 90 min at temperature of 41 °C-42 °C
Verwaal <i>et al.</i> <sup>[36]</sup>	1995-2003	106	Case series (3)	rCPM <sup>2</sup>	-	CRS + HIPEC	Closed abdomen technique	MMC 35 mg/m <sup>2</sup> in 3-4 L of isotonic dialysis fluid at a temperature of 40 °C-41 °C for 90 min
Glehen <i>et al.</i> <sup>[37]</sup>	1989-2002	53	Multicentre case series (3)	CPM <sup>2</sup>	Stage <sup>2</sup> I 13/53 (25) Stage II 8/53 (15) Stage III 7/53 (13) Stage IV 25/53 (47)	CRS + HIPEC	Closed abdomen technique	MMC 40-60 mg in 4-6 L of perfusate at a temperature of 46 °C-48 °C for 90 min
Mahteme <i>et al.</i> <sup>[38]</sup>	1991-1999	36 (18 vs 18)	Case-control (2-)	CPM <sup>2</sup>	-	Treatment arm: CRS + EPIC (n = 18) Control arm: Systemic CT only	Closed abdomen technique	EPIC protocol: 5-FU 550 mg/m <sup>2</sup> in 500 mL normal saline administered intraperitoneally from POD 1. IV infusion of leucovorin (60 mg/m <sup>2</sup> ) commenced at 60 min after initiation of PIC. Regimen offered 1-8 courses as tolerated with 4-6 wk interval between cycles.
Glehen <i>et al.</i> <sup>[38]</sup>	1987-2002	506	Multinational case series (3)	CPM <sup>3</sup>	Limited 171/506 Extended 329/506	CRS + HIPEC and/or EPIC	Open or closed technique	Systemic CT protocol: Chemotherapeutic regimen not specified HIPEC protocol: Various (MMC alone 274/506; MMC + cisplatin 48/506; oxaliplatin 32/506; other 29/506) EPIC protocol: Various (MMC alone 2/506; MMC + 5-FU 113/506; 5-FU alone 95/506; other 7/506)
Shen <i>et al.</i> <sup>[39]</sup>	1991-2002	77	Case series (3)	CPM <sup>3</sup>	-	CRS + HIPEC	Closed abdomen technique	40 mg MMC introduced into dialysis fluid for 120 min at ≥ 38.5 °C
Cavaliere <i>et al.</i> <sup>[40]</sup>	1996-2005	120	Multicentre case series (3)	CPM <sup>1</sup>	-	CRS + HIPEC	Closed abdomen technique	109/120: MMC (3.3 mg/m <sup>2</sup> per liter) and cisplatin (25 mg/m <sup>2</sup> per liter) at 41.5 °C-43 °C for 60-90 min
Kianmanesh <i>et al.</i> <sup>[41]</sup>	1996-2006	43	Case series (3)	CPM <sup>3</sup>	Stage2 I / II 10/43 (23)	CRS + HIPEC	Open technique	11/120: oxaliplatin (460 mg/m <sup>2</sup> ) for 30 min after IV 5-FU and leucovorin MMC 120 mg + cisplatin 200 mg/m <sup>2</sup> at 41 °C-43 °C for 90 to 120 min
Gusani <i>et al.</i> <sup>[42]</sup>	2002-2005	28	Case series (3)	CPM <sup>2</sup>	Stage III 6/43 (14) Stage IV 27/43 (63)	CRS + HIPEC	Closed technique	MMC 30-40 mg in 3 L saline solution at temperature of 40 °C for 100 min
Verwaal <i>et al.</i> <sup>[26]</sup>	1998-2001	105 (54 vs 51)	Randomized trial (1-)	CPM <sup>2</sup>	-	Treatment arm: CRS + HIPEC (n = 54) Control arm: Systemic CT only (n = 51)	Open coliseum technique	HIPEC protocol: MMC 17.5 mg/m <sup>2</sup> at 40 °C for 90 min Systemic CT protocol: 5-FU (400 mg/m <sup>2</sup> ) + leucovorin (80 mg/m <sup>2</sup> ) weekly for 26 wk
Yan <i>et al.</i> <sup>[43]</sup>	1997-2007	50	Case series (3)	CPM <sup>3</sup>	PCI < 10 20/50 PCI 10-20 23/50 PCI > 20 7/50	CRS + HIPEC	Open coliseum technique	MMC 10-12.5 mg/m <sup>2</sup> in 3 L of 1.5% dextrose peritoneal dialysis solution for 90 min at 42 °C

Author	Year	n	Case-control	CPM <sup>1</sup>	Treatment arm: Limited	Treatment arm: CRS + HIPEC	Technique	Protocol
Elias <i>et al.</i> <sup>[54]</sup>	1998-2003	96 (48 vs 48)	Case-control (2-)	CPM <sup>1</sup>	Extended 21/48 Control arm: Limited 26/48 Extended 17/48 Not recorded 5/48	Control arm: Systemic CT only (n = 48)	-	HIPEC protocol: Oxaliplatin 460 mg/m <sup>2</sup> in 2 L/m <sup>2</sup> at 43 °C for 30 min. Before HIPEC (during CRS) patients received IV 5-FU 400 mg/m <sup>2</sup> + leucovorin 20 mg/m <sup>2</sup> Systemic CT protocol: Various regimens (5-FU based 46/48; Capecitabine based 1/48; Campothecin 1/48)
Varban <i>et al.</i> <sup>[63]</sup>	1991-2007	142	Case series (3)	CPM <sup>2</sup>	-	CRS + HIPEC	Closed technique	MMC 40 mg at 40.5 °C-42.5 °C for 120 min
Vaira <i>et al.</i> <sup>[64]</sup>	1997-2008	40	Case series (3)	CPM <sup>2</sup>	PCI > 16 11/40 PCI < 16 29/40	CRS + HIPEC	Closed technique	Cisplatin (100 mg/m <sup>2</sup> ) + MMC (16 mg/m <sup>2</sup> ) at 41.5 °C for 30 min OR Oxaliplatin (460 mg/m <sup>2</sup> ) + IV 5-FU at 42 °C for 30 min OR MMC (35 mg/m <sup>2</sup> ) at 40.5 °C for 60 min
Glehen <i>et al.</i> <sup>[65]</sup>	1989-2007	523	Multi-centre case series (3)	CPM <sup>3</sup>	-	CRS + HIPEC and/or EPIC	Various techniques	HIPEC protocol: MMC (30-50 mg/m <sup>2</sup> ) with or without cisplatin (50-100 mg/m <sup>2</sup> ) delivered over 60-120 min at 41 °C-42.5 °C OR Oxaliplatin (360-460 mg/m <sup>2</sup> ) +/- irinotecan (100-200 mg/m <sup>2</sup> ) +/- IV 5-FU and leucovorin delivered over 30 min at 43 °C OR EPIIC protocol: Abdominal cavity filled at the end of surgery with 1 L/m <sup>2</sup> Ringer lactate. EPIIC lasted 5 d (POD 1-5); POD 1: MMC (10 mg/m <sup>2</sup> ); POD 2-5: 5FU (600 mg/m <sup>2</sup> )
Franko <i>et al.</i> <sup>[65]</sup>	2001-2007	105 (67 vs 38)	Case-control (2-)	CPM <sup>2</sup>	-	Treatment arm: CRS+ HIPEC (n = 67) Control arm: Systemic CT only (n = 38)	Closed abdomen technique	HIPEC protocol: MMC 40 mg for 100 min Systemic CT protocol: Chemotherapeutic regimen(s) not clearly described
Quenet <i>et al.</i> <sup>[66]</sup>	1998-2007	146	Case series (3)	CPM <sup>3</sup>	PCI < 10 69/146	CRS + HIPEC	Closed technique	IV 5-FU (400 mg/m <sup>2</sup> ) + leucovorin (20 mg/m <sup>2</sup> ) followed by: ip oxaliplatin (460 mg/m <sup>2</sup> ) in 2 L/m <sup>2</sup> dextrose OR ip oxaliplatin (300 mg/m <sup>2</sup> ) + ip irinotecan (200 mg/m <sup>2</sup> ) in 2 L/m <sup>2</sup> dextrose
Cashin <i>et al.</i> <sup>[67]</sup>	1993-2008	32 (16 vs 16)	Case-control (2-)	CPM <sup>2</sup>	HIPEC group: Mean PCI 14.4	CRS + HIPEC (n = 16)	HIPEC: Open coliseum technique	HIPEC protocol: Oxaliplatin 460 mg/m <sup>2</sup> for 30 min at 41 °C-42 °C combined with IV 5-FU (450-500 mg/m <sup>2</sup> ) + leucovorin (25-30 mg/m <sup>2</sup> ) EPIIC protocol: 5-FU (500-600 mg/m <sup>2</sup> ) + IV leucovorin (20-30 mg/m <sup>2</sup> ) once daily for 86-d cycles
Passot <i>et al.</i> <sup>[67]</sup>	1991-2010	120	Case series (3)	CPM <sup>3</sup>	Stages I - II 41/120 Stage III-IV 79/120 Mean PCI 8.2	CRS + HIPEC	Closed technique	MMC + irinotecan or oxaliplatin Exact dosing protocol not described
Hompes <i>et al.</i> <sup>[68]</sup>	2004-2008	48	Case series (3)	CPM <sup>2</sup>	Median PCI 11 (1-22)	CRS + HIPEC	Open coliseum technique	IV folic acid (20 mg/m <sup>2</sup> ) + 5-FU (400 mg/m <sup>2</sup> ) followed by ip oxaliplatin (460 mg/m <sup>2</sup> ) in 2 L/m <sup>2</sup> 5% glucose solution at 41 °C-42 °C for 30 min
Cashin <i>et al.</i> <sup>[69]</sup>	1996-2010	151 (69 vs 57)	Case control (2-)	CPM <sup>3</sup>	PCI 1-10 49/151	CRS+ HIPEC (n = 69)	HIPEC: Open coliseum technique	HIPEC protocol: MMC ip (30 mg/m <sup>2</sup> ) for 90 min at 41 °C-42 °C OR oxaliplatin (460 mg/m <sup>2</sup> ) ip for 30 min at 41 °C-42 °C + IV 5-FU (400 mg/m <sup>2</sup> ) and calcium folinate (60 mg/m <sup>2</sup> ) OR oxaliplatin (360 mg/m <sup>2</sup> ) ip + irinotecan (360 mg/m <sup>2</sup> ) for 30 min at 41 °C-42 °C + IV 5-FU (450-500 mg/m <sup>2</sup> ) and calcium folinate (60 mg/m <sup>2</sup> ) EPIIC protocol: 5-FU (500-600 mg/m <sup>2</sup> ) ip + IV leucovorin (60 mg/m <sup>2</sup> ) once daily for 8 6-d cycles

Author	Year	Case series (n)	CPM <sup>1,4</sup>	CRS+ HIPEC (12/24)	Open coliseum technique	HIPEC protocol: <i>ip</i> chemotherapy (MMC or oxaliplatin; dosing not stated) at 42 °C for 90 min EPIC protocol: 5-FU (650-800 mg/m <sup>2</sup> per day) in 1 L 1.5% dextrose for 23 h on POD 1-5
Klaver <i>et al</i> <sup>[69]</sup>	1996-2010	24	-	CRS+ HIPEC (6/24)	Open coliseum technique	EPIC protocol: 5-FU (650-800 mg/m <sup>2</sup> per day) in 1 L 1.5% dextrose for 23 h on POD 1-5
Turrini <i>et al</i> <sup>[50]</sup>	2004-2010	26	-	CRS + HIPEC (6/24)	Open coliseum technique	Oxaliplatin <i>ip</i> (460 mg/m <sup>2</sup> ) in 2 L/m <sup>2</sup> dextrose solution at 43 °C for 30 min after 1 h infusion of IV 5-FU (400 mg/m <sup>2</sup> ) + leucovorin (20 mg/m <sup>2</sup> )
Haslinger <i>et al</i> <sup>[51]</sup>	2003-2011	38	-	CRS+ HIPEC	Closed technique	MMC 40 mg at temperature of 41 °C for 60-120 min
Yonemura <i>et al</i> <sup>[53]</sup>	2004-2012	142	-	CRS + HIPEC	-	MMC 20 mg/m <sup>2</sup> + cisplatin 100 mg/m <sup>2</sup> in \$L saline at 42 °C-43 °C for 60 min

<sup>1</sup>Not stated clearly whether patients with distant metastases to other sites included/excluded; <sup>2</sup>Patients with distant metastases excluded; <sup>3</sup>Cases with extra-abdominal metastatic involvement excluded (LN positive and liver metastasised cases included); <sup>4</sup>All patients ≥ 70 years of age. PCI: Peritoneal cancer index; CRS: Cytoreductive surgery; EPIC: Early post-operative intraperitoneal chemotherapy; POD: Postoperative day; MMC: Mytomycin C; HIPEC: Hyperthermic intra-peritoneal chemotherapy.

failed to meet inclusion criteria and were withdrawn after full text appraisal, leaving 27 studies (1999-2013) for systematic review (Figure 1). The combined number of patients with CPM in these studies was 2838 (range 18-523), of whom 2683 (95%) underwent combined modality treatment involving CRS and IPC. The remaining 155 patients (5%) received systemic chemotherapy alone. Studies included in the review comprised 21 case series<sup>[17,33-52]</sup> (evidence level 3), 5 case-control studies<sup>[53-57]</sup> (evidence level 2-) and 1 randomised controlled trial<sup>[54]</sup> (evidence level 1-). Four studies provided comparative oncological outcome data for patients undergoing CRS in combination with IPC *vs* systemic chemotherapy alone<sup>[26,53-55]</sup>. The primary indication for treatment was CPM in 96% of cases (2714/2838) and recurrent CPM (rCPM) in the remaining 4% (124/2838). Table 1 provides a summary of study design, treatment indications and treatment protocols for studies included in the systematic review process.

### Patient selection

All studies defined first-time treated or recurrent CPM as the primary indication for treatment. Patient selection characteristics with respect to consideration for CRS +/- IPC were stated as follows: Inclusion criteria: (1) CPM of colorectal origin<sup>[17,26,33-57]</sup>; (2) Adequate resection deemed technically feasible based on pre-operative imaging<sup>[34,55,57]</sup>; and (3) Normal marrow indices/renal function/liver function pre-operatively<sup>[26,34,36,43,47,50,56]</sup>.

**Exclusion criteria:** (1) Evidence of extra-abdominal disease on pre-operative imaging<sup>[17,33-38,43-45,47,48,50-54,56,57]</sup>; (2) Evidence of liver metastases on pre-operative imaging<sup>[26,34-37,44,48,51,53,55,57]</sup>; (3) Advanced age (>71 years,<sup>[26,36]</sup> >70 years,<sup>[37,44,47]</sup> >75 years,<sup>[46,50,53]</sup> >80<sup>[17]</sup>); and (4) Significant medical co-morbidity<sup>[34,43,44,46,47,51,52,55,57]</sup>. In the case of the latter criterion, 3 studies used the WHO performance score to determine suitability for aggressive treatment (≥ 2 excluded)<sup>[47,56,57]</sup> and 3 studies used the Eastern Cooperative Oncology Group (ECOG) Performance Status metric<sup>[58]</sup> (≥ 2 excluded)<sup>[46,51,52]</sup>. The remaining 4 studies did not use any formal method for functional assessment<sup>[34,43,44,55]</sup>. None of the identified studies performed formal assessment of functional capacity using cardiopulmonary exercise testing.

### Techniques used for IPC

In the majority of included studies (20/27) CRS was combined with HIPEC<sup>[17,26,34-37,39-44,46-48,50-52,54,55]</sup>. In 3 studies HIPEC was used in combination with EPIC<sup>[37,45,49]</sup>, and 2 studies used EPIC only following cytoreduction<sup>[33,53]</sup>. Two studies were specifically designed to assess comparative outcomes with CRS + HIPEC *vs* CRS + EPIC for treatment of CPM<sup>[56,57]</sup>.

The delivery of IPC was performed using an “open” or “closed” abdomen approach in the included studies. The open approach was generally performed using the Coliseum technique, as proposed by Sugarbaker (Figure 2A)<sup>[59]</sup>. Briefly, this involves placement of a Tenckhoff catheter and four closed suction drains through the abdominal wall before the skin edges are suspended with a running suture to a Thompson self-retaining retractor, creating an open cavity for IPC delivery. Typically, IPC is pumped into the open abdomen *via* the Tenckhoff catheter for between 30-90 min at a temperature of 41 °C-43 °C. This fluid is then circulated back out of the abdomen *via* the four suction drains.

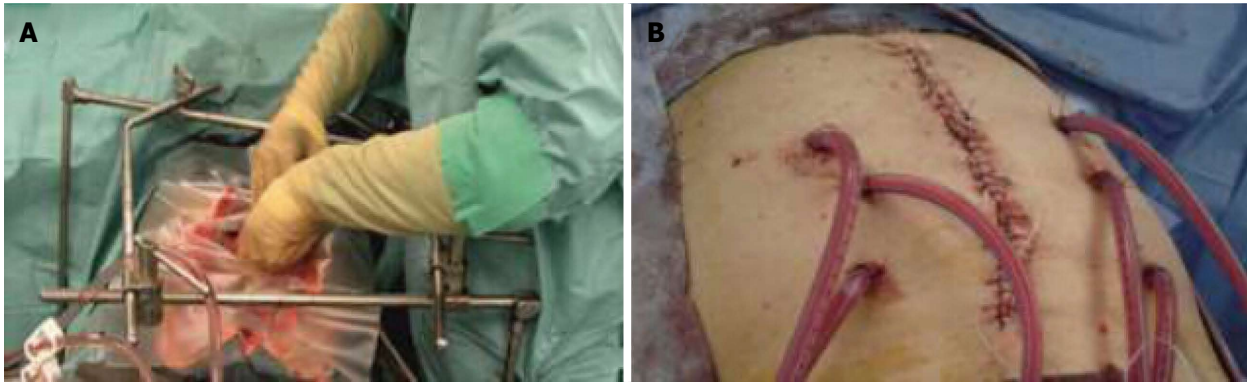


Figure 2 Open (A) and closed (B) methods of intraperitoneal chemotherapy.

The main advantage with this technique is that IPC is distributed evenly throughout the abdomen, though heat dissipation makes it more time consuming to reach the required temperature. With the closed technique catheters are introduced before the laparotomy wound is sutured and perfusion is carried out *via* a closed circuit, with the abdominal wall manually agitated to facilitate even distribution of IPC and temperature (Figure 2B). After adequate perfusion, the abdominal wound is opened in order to evacuate the IPC before re-closure. An advantage with this method is the ability to rapidly achieve the required temperature, as heat dissipation is minimized.

### Oncological outcomes

Oncological outcome data from the 27 studies included in this review are summarised in Table 2. Median survival ranged from 3.7 to 62.7 mo and showed strong correlation with completeness of cytoreduction (as determined by CCS score or R-classification). To date there has been only one RCT carried out to compare outcomes with CRS + HIPEC and conventional systemic chemotherapy alone for treatment of CPM<sup>[26]</sup>. This study included 105 patients randomly assigned to receive either IV 5-FU or experimental treatment which consisted of an aggressive multimodality approach incorporating CRS combined with HIPEC using mitomycin C. After a median follow up time of 96 mo the authors reported median survival of 22.2 mo in the CRS + HIPEC group compared with 12.6 mo in patients receiving chemotherapy alone<sup>[26]</sup>. Three case-control studies provided non-randomized comparative data evaluating the impact of aggressive treatment on survival for patients with CPM. Mahteme *et al.*<sup>[53]</sup> reported outcomes in 18 patients undergoing CRS + EPIC compared with 18 age and gender matched patients receiving chemotherapy only. This study reported overall 2- and 5-year survival of 60% and 28% in the CRS + EPIC group compared with 10% and 5% respectively in the chemotherapy group. Median survival for patients undergoing complete cytoreduction (CC0) was 32 mo compared with 14 mo in the control group. A 2009 study by Elias *et al.*<sup>[54]</sup> reported similarly improved survival with aggressive multi-modality treatment; here the authors compared survival data from 48 patients undergoing CRS

+ HIPEC with 48 receiving chemotherapy alone. Median survival, 2- and 5-year survival were all superior in the CRS + HIPEC treatment group (62.7 mo, 81% and 51%) compared with the chemotherapy group (23.9 mo, 65% and 13%). Franko *et al.*<sup>[55]</sup> reported outcomes of a case-control study of 105 patients with CPM in which 67 underwent CRS + HIPEC and 38 received systemic chemotherapy only. The authors reported 1-, 3- and 5- year survival of 90%, 50% and 25% in the CRS + HIPEC group compared with 55%, 12% and 7% in the control group.

### Complications

Treatment-associated mortality ranged from 0% to 12% in the included studies and overall morbidity was high, ranging from 21.8%-62%. Five of the studies did not provide any morbidity data<sup>[26,33,36,54,55]</sup> and in two studies complications were not reported specifically for patients being treated for CPM<sup>[45,51]</sup>. Specific complications and their incidence are presented in Table 3. The most commonly encountered surgical complications were wound associated problems (infection/dehiscence, 3%-12%)<sup>[34,40-44,49]</sup> fistulae (intestinal/pancreatic/urinary, 1%-11%)<sup>[17,37,38,41-44,46-50]</sup> and intra-abdominal abscess formation (1.8%-14%)<sup>[17,38,41,42,44,46,48]</sup>. The re-operation rate reported from all studies ranged from 4% to 20.8%. Haematological toxicity as a result of chemotherapy was reported with an incidence of 2% to 52%<sup>[34,35,38,39,43,44,48,50,53]</sup>.

## DISCUSSION

Peritoneal metastasis from colorectal cancer (CPM), either at initial presentation, or at subsequent recurrence, presents significant challenges. The majority of patients have extensive disease (correctly labelled colorectal carcinomatosis; Figure 3A), and are not amenable to curative surgical intervention. A proportion, best categorized as Colorectal Peritoneal Metastasis (CPM) (Figure 3B and C) can be treated with curative intent by a combination of CRS and IPC. Without treatment, practically all patients with cancer spread to the peritoneum have poor outcomes, exceptionally impaired quality of life, and abbreviated survival. Conventional surgical resection alone

Table 2 Oncological outcome data *n* (%)

Ref.	Median FU (mth)	Pre-op CT	Post-op CT	Extent of cytoreduction/ disease CCRS <sup>2</sup>	1-yr survival	2-yr survival	3-yr survival	4-yr survival	5-yr survival	Median survival (mo)	Local/distant recurrence
Portilla <i>et al</i> <sup>[33]</sup>	36.2 <sup>1</sup>	22% (regimen not stated)	100% (regimen not stated)	CC0-CC1 (14/18; 64) CC2-CC3 (4/18; 36) PCI < 12 (10/18; 56) PCI > 12 (8/18; 44)	CC0-CC1 (91%) CC2-CC3 (43%) PCI < 12 (N/A) PCI > 12 (N/A)	CC0-CC1 (64%) CC2-CC3 (14%) PCI < 12 (64%) PCI > 12 (14%)	-	-	-	Overall 20	-
Witkamp <i>et al</i> <sup>[34]</sup>	38 (26-52)	-	72% (5-FU+ leucovorin)	-	82%	45%	23%	-	-	-	LR 28% DR 17% LR + DR 28% DR 12% LR + DR 18%
Pilati <i>et al</i> <sup>[35]</sup>	14.5 (6-34)	0%	-	CC0-1 34/34	68%	31%	-	-	-	18	LR 59% DR 12% LR + DR 18%
Verwaal <i>et al</i> <sup>[36]</sup>	47.5 (1.3-88.3)	-	15% (leucovorin)	R1 (54/106; 51) R2a (37/106; 35) R2b (15/106; 14) CC0 (23/53; 43) CC1 (11/53; 21) CC2 (19/53; 36) CC0 (11/18; 61)	-	-	-	-	-	R1 11.1 R2a 5.9 R2b 3.7 CC0 32.9 CC1 12.5 CC2 8.1	Unspecified recurrence 65%
Glehen <i>et al</i> <sup>[37]</sup>	59.5	-	68% (5-FU + irinotecan leucovorin)	CC0 (23/53; 43) CC1 (11/53; 21) CC2 (19/53; 36) CC0 (11/18; 61)	CC0 85% CC1 46% CC2 24%	CC0 54% CC1 36% CC2 0%	-	-	CC0 22% CC1 9% CC2 0%	CC0 32.9 CC1 12.5 CC2 8.1	Unspecified recurrence 19%
Mahteme <i>et al</i> <sup>[38]</sup>	-	-	-	CC0 (11/18; 61)	-	CRS + EPIC 60%	-	-	CRS + EPIC 28%	CRS + EPIC overall 28%; CC0 34.5 CC1-2 10	-
Glehen <i>et al</i> <sup>[38]</sup>	53	54%	40%	CC1-2 (7/18; 39) CC0 (271/506; 54) CC1 (106/506; 21) CC2 (129/506; 25)	CC0 87% CC1 79% CC2 38%	-	CC0 47% CC1 29% CC2 6%	-	Control arm 5% CC0 31% CC1 15% CC2 0%	Control arm: 14 Males 16.8 Females 21.6	Unspecified recurrence 73%
Shen <i>et al</i> <sup>[39]</sup>	15 (3-85)	75%	-	R0 (13/77; 17) R1 (24/77; 31) R2a (11/77; 14) R2b (9/77; 12) R2c (20/77; 26) CC1 (9/120; 7) CC2-3 (9/120; 7)	-	-	R0 69% R1 19% R2a 28% R2b 0% R2c 6%	-	R0 55% R1 19% R2a 14% R2b 0% R2c 0%	R0 N/R R1 17.8 R2a 12.7 R2b 4.1 R2c 5.0	Unspecified recurrence 68%
Cavaliere <i>et al</i> <sup>[40]</sup>	16	72%	-	CC0 (102/120; 85) CC1 (9/120; 7) CC2-3 (9/120; 7)	-	-	Overall 25.8% CC0 33.5%	-	-	Overall 19	-
Kiamanesh <i>et al</i> <sup>[41]</sup>	-	70%	75%	-	-	72%	44%	-	-	38.4	-
Gusani <i>et al</i> <sup>[42]</sup>	35.9 (19-57.7)	-	-	-	78%	37%	-	-	-	15.2	-
Verwaal <i>et al</i> <sup>[26]</sup>	96 (72-115)	-	-	R1 (22/54; 41) R2a (23/54; 43) R2b (9/54; 17)	R1 95% R2a 65% R2b 22%	R1 80% R2a 20% R2b 12%	R1 52% R2a 10% R2b 0%	R1 45% R2a 10% R2b 0%	CRS + HIPEC R2a 10% R2b 0%	CRS + HIPEC Systemic CT 12.6	-
Yan <sup>[17]</sup>	14 (1-56)	-	-	CC0 (41/50; 82) CC1-3 (9/50; 8)	CC0 85% CC1-3 51%	-	CC0 62% CC1-3 0%	-	-	CC0 37 CC1-3 14	Unspecified recurrence 34%



Elias <i>et al</i> <sup>[54]</sup>	95.7	-	-	-	CRS + HIPEC	-	-	CRS + HIPEC	-	CRS + HIPEC	-
Varban <i>et al</i> <sup>[43]</sup>	14.6	-	-	-	81% Systemic CT	51% Systemic CT	13% Systemic CT	62.7 Systemic CT	62.7 Systemic CT	62.7 Systemic CT	-
Vaira <i>et al</i> <sup>[44]</sup>	-	55%	-	-	HM 43.3% No HM 36.8%	HM 14.4% No HM 17.4%	-	HM 23 No HM 15.8	HM 23 No HM 15.8	HM 23 No HM 15.8	-
Glehen <i>et al</i> <sup>[45]</sup> Franko <i>et al</i> <sup>[55]</sup>	-	-	100	-	58% CRS + HIPEC	39% CRS + HIPEC	34% CRS + HIPEC	28% CRS + HIPEC	28% CRS + HIPEC	28% CRS + HIPEC	-
Quenet <i>et al</i> <sup>[46]</sup>	48.5	100%	-	-	65% Systemic CT	50% Systemic CT	42% Systemic CT	25% Systemic CT	34.7 Systemic CT	34.7 Systemic CT	Unspecified recurrence 70%
Cashin <i>et al</i> <sup>[56]</sup>	HIPEC	HIPEC	HIPEC	-	90% Systemic CT	55% Overall	12% Overall	10% Overall	7% Overall	16.8 Overall	41
Passot <i>et al</i> <sup>[47]</sup>	58.5 (1-183)	75%	64.30%	-	78% EPIC group	48% EPIC group	17% EPIC group	17% EPIC group	33% Overall	36.2 Overall	-
Hompes <i>et al</i> <sup>[48]</sup>	22.7 (3.2-55.7)	-	62.50%	-	OS 98% DFS 66%	OS 89% DFS 46%	-	-	-	-	-
Cashin <i>et al</i> <sup>[57]</sup>	49 (0.5-100)	31%	18%	-	HIPEC	HIPEC	HIPEC	HIPEC	-	HIPEC	-
Klaver <i>et al</i> <sup>[49]</sup>	10.5 (1-52)	-	-	-	80% EPIC	50% EPIC	27% EPIC	18% EPIC	34 EPIC	34 EPIC	-
Turrini <i>et al</i> <sup>[50]</sup> Haslinger <i>et al</i> <sup>[51]</sup>	-	-	-	-	5% Overall	83% Overall	100% Overall	51% Overall	37% Overall	25 Overall	Unspecified recurrence 54%
Yonemura <i>et al</i> <sup>[52]</sup>	-	77%	-	-	CC0 (22/24; 92) CC1 (2/24; 8)	CC0 (108/142; 76) CC1 34/142 (24)	-	-	OS 38% PFS15%	24.4 CC0 25.9 CCI 9.9%	-

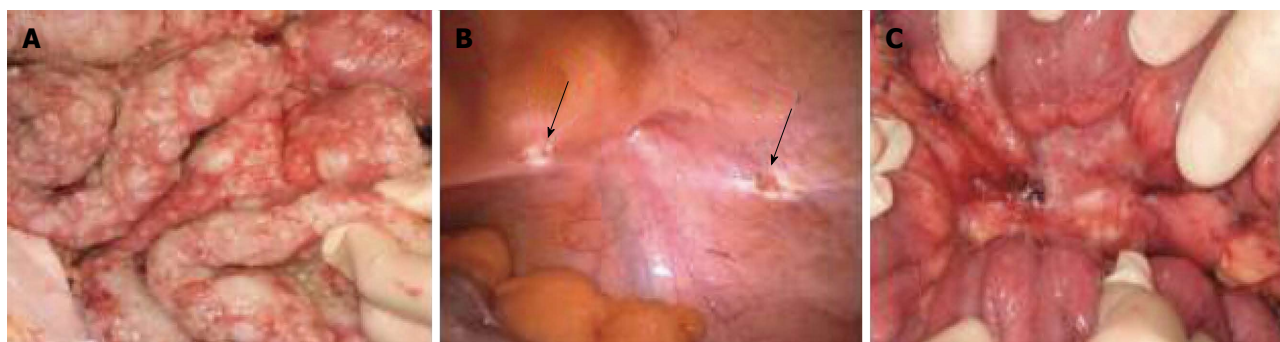
<sup>1</sup>Peritoneal cancer index (PCI) - Calculated by combining lesion size (0-3; 0-no nodules present, 1-nodule(s) ≤ 5 mm diameter, 2-nodule(s) 5-50 mm in diameter, 3-nodule(s) ≥ 50 mm in diameter) with the abdominopelvic regions affected<sup>[43]</sup>; <sup>2</sup>Completeness of cytoreduction score (CCRS)<sup>[53]</sup>; CC0 No visible tumour remaining; CC1 residual tumour deposits < 2.5 mm in diameter; CC2 residual tumour deposits 2.5-25 mm in diameter; CC3 residual tumour deposits > 25 mm in diameter. HIPEC: Hyperthermic intraperitoneal chemotherapy; EPIC: Early post-operative intraperitoneal chemotherapy; CRS: Cytoreductive surgery; CT: Computed tomography.

**Table 3** Reported treatment-associated morbidity and mortality following multi-modality therapy for colorectal peritoneal metastase

Ref.	n	Mortality (%)	Overall morbidity (%)	No of bowel anastomoses	Intra-abdominal complications (%)	Extra-abdominal complications (%)
Portilla <i>et al</i> <sup>[33]</sup>	18	0			No treatment-associated morbidity data provided	
Witkamp <i>et al</i> <sup>[34]</sup>	29	3	38	2 (0-5)	Postoperative bleeding (3) Bowel perforation (3) Bladder perforation (3) Return to theatre (17) Hydronephrosis requiring nephrostomy (7) Wound dehiscence (3) Prolonged chyle leak (3)	Grade I - II leucopenia (21) Grade III leucopenia (31) Peripheral neuropathy (10) Subclavian vein thrombosis (3)
Pilati <i>et al</i> <sup>[35]</sup>	34	0	35	-	Non-specified complications: Ozols' grade I (53), grade II (9), grade III (1), grade IV (1)	Haematological toxicity (12) Pneumonia (12)
Verwaal <i>et al</i> <sup>[36]</sup>	106	-			No treatment-associated morbidity data provided	
Glehen <i>et al</i> <sup>[37]</sup>	53	4	23	0.4 (0-4)	Return to theatre (4) Gastrointestinal fistula (8)	-
Mahteme <i>et al</i> <sup>[53]</sup>	18	0	61	-	Severe nausea and vomiting (12) Leak from drain (6) Catheter-related problems (39)	Transient neutropaenia (6)
Glehen <i>et al</i> <sup>[38]</sup>	506	4%	22.9	-	Re-operation (10.7) Fistula (8.3) Intra-abdominal abscess (1.8) Urinary fistula (1)	Haematological toxicity (2.4) Systemic sepsis (2) Cardiorespiratory complications (3.5)
Shen <i>et al</i> <sup>[39]</sup>	77	12	30	-	Bowel perforation (3)	Haematological toxicity (19)
Cavaliere <i>et al</i> <sup>[40]</sup>	120	3.3	22.5	-	Perforation (5) Anastomotic leak (3.3) Infection (3.3)	
Kianmanesh <i>et al</i> <sup>[41]</sup>	43	2.3	39	-	Deep abscess (14) Intestinal fistula (9) Delayed gastric emptying (9)	Pleural effusion (12) Renal failure (7) Superficial wound infection (12)
Gusani <i>et al</i> <sup>[42]</sup>	28	0	56.5	-	Re-operation (4) Re-operation (8) Anastomotic leak (8) Intra-abdominal abscess (4) Wound dehiscence (4) Enterocutaneous fistula (2)	Systemic sepsis (4)
Verwaal <i>et al</i> <sup>[26]</sup>	54	-			No treatment-associated morbidity data provided	
Yan <sup>[17]</sup>	50	0	46	-	Small bowel obstruction (12) Fistula (10) Intra-abdominal abscess (10) Perforation (4)	Pleural effusion (34) Pneumonia (4)
Elias <i>et al</i> <sup>[54]</sup>	48	-			No treatment-associated morbidity data provided	
Varban <i>et al</i> <sup>[43]</sup>	142	CPM with HM 7.1% CPM with no HM 7.7%	CPM with HM 57.1% CPM with no HM 40.1%	-	CPM with HM Bowel leak (11) Wound infection (11) Pancreatic fistula (11) Ileus (11) CPM with no HM Bowel leak (5) Wound infection (5) Ileus (5) Enterocutaneous fistula (1)	CPM with HM Pneumonia (7) Neutropaenia (7) DVT (7) CPM with no HM Pneumonia (6) Neutropaenia (8) AF (3) Thrombocytopenia (2)
Vaira <i>et al</i> <sup>[44]</sup>	40	2.5	55	0 (17.5) 1(55) 2 (27.5)	Fistula (10) Abdominal abscess (7.5)	Haematological toxicity (12.5) Pleural effusion (22.5) Superficial wound infection (12.5)
Glehen <i>et al</i> <sup>[45]</sup>	523	-			Not specifically provided for patients undergoing procedures for CPM	
Franko <i>et al</i> <sup>[55]</sup>	105	-			No treatment-associated morbidity data provided	
Quenet <i>et al</i> <sup>[46]</sup>	146	4.1	47.2	-	GI fistula (4.8) Urinary fistula (1.4) Abdominal abscess (2.7) Reoperation (11.6)	-
Cashin <i>et al</i> <sup>[57]</sup>	32	HIPEC group; 6% EPIC group; 6%	HIPEC group; 37% EPIC group; 19%	-	HIPEC group; Reoperation (12) EPIC group; Reoperation (6)	HIPEC group; CVA (6) EPIC group; -

Passot <i>et al</i> <sup>[47]</sup>	120	3.8	21.8	-	Reoperation (13.3) Fistula (7.5)	
Hompes <i>et al</i> <sup>[48]</sup>	48	0	52.1	1 (0-6)	Prolonged ileus (23) Anastomotic leakage (10.4) Bleeding (6.3) Bowel perforation (2.1) Fistula (2.1) Abscess (2.1) Reoperation (20.8)	Pulmonary (12.5) Cardiac (2.1) Urological (12.5) Haematological (2.5)
Cashin <i>et al</i> <sup>[56]</sup>	151	HIPEC group: 4%	HIPEC group: 41%	-	-	-
		EPIC group: 3%	EPIC group: 30%			
Klaver <i>et al</i> <sup>[49]</sup>	24	0	62	-	Prolonged ileus (21) Intra-abdominal collection requiring drainage (21) Fistula (4) Splenic infarction (4) Fistula (10) Delayed gastric emptying (10)	Superficial wound infection (4) Cardiorespiratory complications (38) Urological (4)
Turrini <i>et al</i> <sup>[50]</sup>	26	0	33	-	Fistula (10) Delayed gastric emptying (10)	Haematological toxicity (10)
Haslinger <i>et al</i> <sup>[51]</sup>	38	-	-	-	Not specifically provided for patients undergoing procedures for CPM	
Yonemura <i>et al</i> <sup>[52]</sup>	142	0.7	42.9	-	-	-

CPM: Colorectal peritoneal metastase; HM: Hepatic metastasis; HIPEC: Hyperthermic intraperitoneal chemotherapy; EPIC: Early post-operative intraperitoneal chemotherapy.



**Figure 3** Widespread colorectal peritoneal carcinomatosis (A) compared to colorectal peritoneal metastasis on the parietal peritoneal surface (B, arrows) or on the peritoneum of the small bowel mesentery (C).

has not been demonstrated to be effective for treatment of CPM, and is associated with a median survival of less than 6 mo<sup>[60]</sup>. Similarly, orthodox systemic chemotherapy treatment for CPM has only limited efficacy, at least in part owing to the plasma-peritoneal barrier which results in decreased intra-peritoneal drug penetration.

For all these reasons, aggressive multidisciplinary treatment incorporating cytoreductive surgical (CRS) techniques and intra-peritoneal chemotherapy has been proposed and pursued as a logical treatment strategy to improve long-term survival, and may represent an appealing and natural evolution of the management of complex and advanced CRC.

Historically, this form of radical approach has been rarely applied owing to concerns regarding high morbidity and mortality. In more recent times however, advances in radiological staging and surgical and anaesthetic practice, improved experience in chemotherapeutic methods, and better management of associated toxicity, have helped expand the treatment options for patients with peritoneal disease, allowing enhanced prognosis and sur-

ivorship through increased application of CRS and IPC. However, despite a recent consensus statement published on the role of CRS in combination with HIPEC in the management of CPM<sup>[24]</sup>, there is on-going disagreement and controversy regarding the precise role of this multimodality approach in treatment algorithms, and firm evidence to support widespread implementation has been questioned.

The purpose of the present review was to systematically and critically analyse the available literature. Twenty seven studies with a combined population of 2838 patients met the predefined inclusion criteria and were included in the review process. Only publications in the last 15 years were included to eliminate any time-dependant bias from subtle alterations to treatment approaches and drugs. The available literature consists mainly of low-grade evidence with small case series or comparative studies, with the exception of one relatively recent randomised trial. Furthermore, there is substantial between-study heterogeneity, non-standardised definitions, and inconsistent reporting of data. In spite of these limita-

tions, this body of data clearly indicates that the greatest survival times from CPM are achieved after treatment in specialist institutions by CRS and IPC, with a predictable high, but perhaps acceptable, frequency of complications. The exact nature and location of re-recurrence was reported in few studies, with disease recurring in the peritoneal compartment (ranging from 28%-59%); in distant organs alone (12%-17%); or in both peritoneal and distant organs (18%-28%; Table 2).

One key consideration is the selection of patients for radical treatment strategies. The studies included in this review illustrate a wide variety of methods with no overall consensus or approach. While a number of studies stated medical co-morbidity as one exclusion criterion, this was generally poorly defined. Cardiopulmonary exercise testing is one of the most reliable methods of risk prediction in non-cardiopulmonary surgical procedures, outperforming alternative methods of risk stratification, and can readily aid in identification of patients at an increased risk of adverse perioperative events<sup>[61]</sup>. No studies included in the present review used formal pre-operative cardiopulmonary exercise testing as a risk stratification measure however. Similarly, while some authors would consider the presence of other solid organ metastases on pre-operative imaging to be a contraindication to CRS and PIC<sup>[26,34-37,42,44,48,51,53,55,57]</sup> this is not an absolute if other metastases are resectable<sup>[38]</sup>. Further stratification factors are the extent of disease, and the ability to achieve a complete cytoreduction. Both are major predictors of oncological outcome, however significant variability was noted in the assessment methods used for the evaluation of disease extent in the studies examined. In 10 of the included studies a marked reduction in long-term survival was reported following CC2-3, compared with CC0-1 resection<sup>[26,33,36-39,44,52,53,62]</sup>. In the largest study included in this review, analysis of outcomes in 506 patients treated with CRS and HIPEC found completeness of cytoreduction to be the strongest predictor of survival on multivariate analysis ( $P < 0.0001$ )<sup>[38]</sup>. The authors of this study also found extent of disease at time of surgery (PCI) to be a significant determinant of survival ( $P < 0.001$ )<sup>[38]</sup>. This finding is supported by the results of Quenet *et al*<sup>[46]</sup> who reported 5-year survival of 65%, 26% and 18% respectively for patients with PCI < 10, PCI 11-19 and PCI > 20. Other factors such as tumour differentiation<sup>[17,35,38,52]</sup> the presence of bowel obstruction<sup>[39]</sup>, malignant ascites<sup>[39]</sup>, age<sup>[38]</sup> lymph node dissemination<sup>[38]</sup> and extent of small bowel involvement<sup>[52]</sup> have also been identified as negative prognostic indicators, and further investigation is required in order to better define the relative contributions of these factors to disease outcome.

The present systematic analysis is subject to a number of limitations. All but one of the studies were non-randomised, mainly with small sample sizes, and were heterogeneous with respect to extent of peritoneal disease and its manner of assessment; protocol and type of chemotherapy applied; and measured outcomes. Most were conducted in large tertiary referral cancer centres.

Crucially, it is not possible to separate the incremental contribution of CRS and IPC from the available data, making it difficult to draw definitive conclusions regarding the individual contribution of each to the positive outcomes. Only one RCT has been undertaken to date comparing CRS and IPC with conventional systemic chemotherapy<sup>[26]</sup>. Verwaal *et al*<sup>[26]</sup> found improved survival with CRS + HIPEC compared with systemic chemotherapy alone, though these findings are limited somewhat by the single institution nature of the study, the relatively modest sample size, and the fact that patients in the control arm received 5-FU, rather than more contemporary oxaliplatin-based therapy. Clearly therefore, the findings presented here must be interpreted within these limitations. Nevertheless, in view of the limited evidence base in this field at the present time, synthesised evidence in the present form represents the most informative means of evaluation.

A number of questions still remain. Better methods of patient selection are clearly required, and the role of physiological testing preoperatively may well merit further study to more effectively gauge functional capacity and risk of adverse events. In addition, an important challenge in the future will be to identify methods to avoid over-treatment in patients with chemotherapy insensitive tumours, and to limit side-effects in those with chemo-sensitive disease. The exact type of chemotherapy and its method of administration remain unclear at the present time, as is the precise contribution of CRS and IPC to the favourable outcomes observed. A further key question will be whether different/more radical/dose escalated IPC regimes can counter unfavourable peritoneal disease extent scores. Robust molecular biomarkers of oncological outcome and disease response are clearly required and are presently lacking. Exciting developments in the molecular sciences and the multi-platform high-throughput methods increasingly applied to diverse tumour types are transforming established treatment approaches, and offer the opportunity for the development of more personalised strategies in the treatment of CPM. Although no targeted therapeutic agents are currently approved for use in the treatment of CPM, it is expected that emerging tumour-targeted molecular therapies will permit more cancer-specific cytotoxicity, potentially enhancing oncological outcome and minimising unwanted toxicity.

In conclusion, Peritoneal disease from colorectal cancer remains a significant clinical problem and presents unique challenges and opportunities. The concept of resectable CPM is useful in this complex field. The present review indicates that the evidence base for CRS and IPC is composed largely of prospective and retrospective series with only one RCT on the subject to date. Nevertheless these studies appear to demonstrate survival rates greater than any available alternative, justifying an aggressive approach. Similar to acceptance of surgery for liver, lung, and occasionally brain metastatic CRC, radical treatment for peritoneal disease from CRC now has an

established place in selected patients, offering the only realistic chance of long-term survival. In the future, high-number, multi-institutional studies with limited heterogeneity in assessment and treatment protocols may better enable clarification of some of the controversies in the treatment of CPM.

## COMMENTS

### Background

The finding of peritoneal surface malignancy in the context of colorectal cancer confers a dismal prognosis. Conventional treatment for this sub-group of patients involves systemic chemotherapy with or without palliative surgery. Multimodality treatment with cytoreductive surgery in combination with intraoperative chemotherapy is performed at specialist units around the world and can result in improved oncological outcome.

### Research frontiers

The aim of cytoreductive surgery (CRS) is to remove all macroscopic disease through peritonectomy and multi-visceral resections where required. The extensiveness of these approaches varies according to cancer volume and anatomical location. The combination of CRS with intraperitoneal chemotherapy (IPC) has been advocated in order to eradicate residual cancer cells after macroscopic cytoreduction. In this study, the authors provide a Systematic Review of the available evidence regarding these multimodality treatment approaches.

### Innovations and breakthroughs

Recent reports indicate that combined therapy involving CRS and IPC can result in improved oncological outcome and even long-term survival in patients with colorectal peritoneal metastases (CPM), compared to conventional treatment. This study provides a comprehensive and up-to-date review of the available literature in this field.

### Applications

Although subject to inherent methodological limitations, the studies included in this review appear to support the use of an aggressive multimodality treatment approach in the management of CPM.

### Terminology

CRS refers to the macroscopic removal of peritoneal surface cancer deposits through peritoneal stripping procedures and/or visceral resection, depending on extent and location of carcinomatosis. Intraperitoneal chemotherapy is administered in combination with CRS as a means of eradicating residual tumour.

### Peer review

The authors present a systematic review of the literature of cytoreductive surgery combined with intraperitoneal chemotherapy in colorectal cancer peritoneal metastasis. The authors spent a lot of efforts on the summary of clinical data from 27 studies. It has been reported the effectiveness of intraperitoneal chemotherapy in the patients with peritoneal metastasis. However, this kind of review work has not been reported. Therefore, this work has very high originality to contribute to the further clinical works.

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