Ann Surg Oncol (2009) 16:2152–2165
DOI 10.1245/s10434-009-0487-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

A Systematic Review and Meta-Analysis of Cytoreductive Surgery with Perioperative Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis of Colorectal Origin

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ABSTRACT

Background. The objective of the present meta-analysis was to analyze the survival outcomes of patients with colorectal peritoneal carcinomatosis (CRPC), with particular focus on cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC).

Methods. A search was conducted on Medline from 1950 to February 2009 and Pubmed from 1950 to February 2009 for original studies on CRS with PIC. All articles included in this study were assessed with the application of predetermined selection criteria. Results regarding the overall survival in the meta-analysis were expressed as hazard ratios with 95% confidence intervals.

Results. Forty-seven manuscripts were selected in the present systematic review, including 4 comparative studies and 43 observational studies of CRS with PIC. From the meta-analysis, it can be seen that a significant improvement in survival was associated with treatment by CRS and hyperthermic intraperitoneal chemotherapy compared with palliative approach ($P < 0.0001$). The pooled data did not show a significant improvement in overall survival for patients treated by CRS and early postoperative intraperitoneal chemotherapy versus surgery and systemic chemotherapy ($P = 0.35$). The overall effect of PIC is significantly better than the control group ($P = 0.0002$). The current literature suggests that patients with liver metastasis amendable to resection should not be excluded from CRS and PIC. However, there is a need for further evaluation of the prognostic significance of lymph node and liver involvement, ideally in large prospective trials.

Conclusions. The meta-analysis showed that combined therapy involving CRS and PIC had a statistically significant survival benefit over control groups.

First Received: 8 January 2009;
Published Online: 12 May 2009

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Colorectal peritoneal carcinomatosis (CRPC) is a common clinical phenomenon in patients with colorectal cancer and has been reported to have a poor prognosis in the past. Approximately 5–10% of patients with colorectal carcinoma present with synchronous metastases of the peritoneum at the time of initial colon resection and 20–50% may present with metachronous disease.[1,2] Traditional treatment consisted of systemic chemotherapy, with or without palliative surgery, resulting in a median survival of less than 6 months.[1–3] Despite the development of modern regimens such as folinic acid/leucovorin (LV), 5-flurouracil (5-FU), and oxaliplatin (FOLFOX), long-term survival for patients with advanced colorectal metastases has not been achieved.[4]

Since the 1990s, studies on cytoreduction surgery (CRS) followed by perioperative intraperitoneal chemotherapy (PIC), i.e. hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC), have prompted a new treatment option for selected patients with CRPC.[5–51] The addition of PIC aims to eradicate residual tumor cells after macroscopic surgical cytoreduction. However, concerns about the perioperative morbidity and mortality of this management plan, as well as its efficacy, have delayed a consensus in its practice. The polarity of opinion amongst the medical community has been long standing, resulting in a deepening stalemate. On one hand, surgeons familiar with CRS and PIC are reluctant to perform further randomized controlled trials (RCTs) in the absence of any evidence demonstrating efficacy of systemic chemotherapy for isolated CRPC. To date, there has been one completed RCT

assessing CRS and HIPEC versus systemic chemotherapy and debulking surgery, which demonstrated superior survival outcome in the combined treatment modality group.[5] However, others insist on more trials using newer chemotherapeutic agents, with or without biological agents.

In addition to disagreement about the overall efficacy of CRS and HIPEC, there is a paucity of robust data regarding the prognostic significance of liver and lymph node metastasis in CRPC. Previously, metastasis of colorectal carcinoma to the liver was an exclusion criterion for CRS in a number of clinical trials for patients with CRPC. However, several studies have shown no significant impact on the outcome for these patients after resection. The importance of lymph node involvement is similarly unclear.

Due to the lack of further RCTs, performing a meta-analysis including RCTs and comparative studies will help determine the efficacy of CRS with PIC in the current medical setting. The objective of the present meta-analysis was to analyze the survival outcomes of patients with CRPC, with particular focus on CRS and PIC. In addition, a systematic literature review on the prognostic significance of liver and lymph node metastasis in patients with CRPC was performed.

METHODS

Literature Search Strategy

A search was conducted on Medline from 1950 to February 2009 and Pubmed from 1950 to February 2009 for original studies on CRS with PIC. All articles included in this study were assessed with the application of predetermined selection criteria. In addition, the reference lists of all selected studies were reviewed for further identification of potential relevant articles. When studies overlapped or duplicated, those articles with more complete data on CRS and PIC were retained.

Selection Criteria

Inclusion criteria included all articles concerning histopathologically defined CRPC treated by CRS, HIPEC, EPIC or a combination of these modalities. Studies were limited to human trials, and in English language. Exclusion criteria included studies consisting of more than 20% PC of appendiceal origin, as previous studies have shown significant differences in the behavior and prognosis of appendiceal carcinomas compared with colorectal carcinomas.[12] Similarly, data regarding tumors without specific documentation of colorectal origin were not included. However, these exclusions were not applied if isolated data regarding CRPC are provided. Case studies, review articles, and studies involving fewer than ten patients were excluded to allow consistent results.

The aim of CRS procedures was to remove all visible evidence of tumor within the abdominal cavity. Six different peritonectomy procedures were used in various combinations on patients. These included: (1) greater omentectomy with splenectomy, (2) left upper quadrant peritonectomy, (3) right upper quadrant peritonectomy, (4) lesser omentectomy with cholecystectomy, (5) pelvic peritonectomy with resection of the rectosigmoid colon, and (6) antrectomy.[52]

HIPEC was achieved by insertion of an intraperitoneal catheter and suction drains through the abdomen, followed by running a large volume of chemotherapeutic agents through the abdominal cavity via continuous infusion using a roller pump. This was conducted either via closed or open techniques for a period of 30–120 min at an intraperitoneal temperature of 40–44°C during the CRS procedure. In some studies, EPIC was subsequently given on postoperative day (POD) 2–7, consisting of normothermic intraperitoneal chemotherapy of various regimens.

Data Extraction and Critical Appraisal

Two reviewers independently reviewed each article, and discrepancies were resolved by discussion and consensus. All data were extracted from article texts, tables, and figures. Studies were evaluated for their chemotherapeutic regimens, their yearly survival up to 5 years after intervention, median survival, morbidity rates, hospital stay, follow-up, and involvement of liver or lymph node metastasis. The studies were categorized into five levels of evidence as set out by the Oxford Centre for Evidence-Based Medicine Levels of Evidence: level 1, systematic reviews of randomized controlled trials (RCTs), individual RCTs with narrow confidence interval, studies with "all or none" results; level 2, systematic reviews of cohort studies, individual cohort studies, low-quality RCTs, "outcome" research; level 3, systematic reviews of case–control studies, individual case–control study; level 4, case series, poor-quality cohort and case–control studies; level 5, expert opinion.[53]

Statistical Analysis

The end-point of the meta-analysis was overall survival, defined as time from the surgical procedure to the last follow-up or death. There were four suitable studies that compared combined treatment involving CRS and PIC with controls.[5–8] The study by Verwaal et al. involved 54

patients who underwent CRS and HIPEC followed by systemic chemotherapy, compared with 51 patients who had systemic chemotherapy and palliative surgery.[5] Elias and colleagues compared CRS, EPIC, and systemic chemotherapy with CRS and systemic chemotherapy.[6] Another more recent study by Elias et al. compared two groups of 48 patients who either had CRS, HIPEC, and systemic chemotherapy or systemic chemotherapy alone.[7] Mahteme et al. recorded 18 patients who had CRS and EPIC with systemic chemotherapy, and compared them with a matched group of patients in the control arm, who underwent palliative surgery and systemic chemotherapy.[8]

Results regarding the overall survival in the meta-analysis were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Verwaal, et al. stated HR and its variance in their study, and these values were directly extracted for the meta-analysis.[5] In the studies conducted by Elias and Mahteme, HR and CI were calculated from data presented using a hierarchical series of steps as per Parmar et al.[6–8,54] Survival rates were extracted at specified times in order to reconstruct the HR estimate and its variance. Survival curves were read independently by the two investigators.

χ^2 tests were used to study heterogeneity between trials. *I*-squared statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. Even though values below 25% are considered to represent low heterogeneity, this interpretation can have a large degree of uncertainty in the presence of only a few trials.[55] All statistical analysis was conducted by using Review Manager (RevMan) version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008).

RESULTS

Quantity of Evidence

Review of abstracts from 855 articles on Medline and Pubmed resulted in 80 potentially relevant publications. Experts in peritoneal surface malignancy identified five more recent articles. Assessment of these 85 articles using the inclusion and exclusion criteria resulted in 47 papers that qualified for the overview (Table 1).[5–51] Of these, a number of studies focused on peritoneal carcinomatosis of numerous origins with a subset of CRPC patients comprising less than half of all patients.[11,17,23,27,28,30,32,33,35,42,45–47,51]

Quality of Evidence

To date, the only completed RCT was conducted by Verwaal et al., who compared CRS and HIPEC with chemotherapy and palliative surgery.[5] The process of concealed randomization in this study was adequately implemented, and baseline prognostic factors appeared to be similar. Randomization was stratified according to presentation (primary versus recurrence) and site (appendix, rectum, and colon). Eighteen of the 105 patients included in the study had PC from appendiceal adenocarcinoma, and isolated data regarding CRPC could not be extracted. One patient was lost to follow-up after 7 months. Eligibility criteria were clearly stated. All patients, including ineligible ones, were included in the intention-to-treat analysis.

The other attempted RCT included in this review was by Elias et al., who conducted a two-centre prospective trial comparing CRS, EPIC, and systemic chemotherapy with CRS and systemic chemotherapy alone.[6] Unfortunately, only 35 patients could be enrolled in this trial and it was terminated before reaching the required 90 patients. There was no statement regarding the process of concealed randomization or stratification. Baseline prognostic factors appeared to differ in the two arms. Eligibility criteria were clearly defined. Patients lost to follow-up and blinding were not documented.

Another retrospective comparative study by Elias et al. involved two groups of 48 patients who either had CRS, HIPEC, and systemic chemotherapy, or systemic chemotherapy alone.[7] Chemotherapeutic agents used in this study included modern agents such as oxaliplatin, which was used in HIPEC as well as systemic chemotherapy for both the control and experimental groups. The control group was selected retrospectively with the same inclusion criteria as the experimental group, and the authors acknowledged differences in age and tumor differentiation between the two groups. Perioperative mortality and morbidity were not clearly stated.

Mahteme et al. compared 18 patients with CRPC treated by CRS, EPIC (5-FU, cisplatin, or irinotecan), and systemic chemotherapy with 18 matched patients in the control group, who were treated by systemic chemotherapy only.[8] The control group were randomly selected from Nordic chemotherapy trials and matched according to gender, age, performance status, and metastatic site. Duration and dosage of intravenous chemotherapy in the control group were not clearly defined. Selection bias cannot be ruled out. There was no information on follow-up in either group.

Forty-three of the 47 publications found in this review were observational studies of CRS with HIPEC or EPIC. Of these, 40 were single-institutional studies from isolated tertiary centers specialized in peritonectomy procedures.[12–51] Three were multicenter studies, conducted by Elias, Glehen, and Gomez.[9–11] It should be noted that, although the study by Gomez et al. included 266 patients

TABLE 1 Systematic review of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC) with or without systemic chemotherapy (SC) for patients with colorectal peritoneal carcinomatosis (CRPC)

Author and year	Study period	Evidence	Intervention	Study sample (CRC%)	Follow-up (months)
Verwaal et al.[5]	1998–2001	Level 1b	SC ± palliative surgery vs. CRS + HIPEC + SC	105 (83%) 51 vs. 54	21.6
Elias et al.[6]	1996–2000	Level 2b	EPIC + SC vs. SC	35 (86%) 16 vs. 19	N/A
Elias et al.[7]	1998–2003	Level 2b	CRS + HIPEC + SC vs. SC ± debulking surgery	48 vs. 48	63 vs. 95.7
Mahteme et al.[8]	1991–1999	Level 2b	CRS + EPIC vs. debulking surgery + SC	18	N/A
Elias et al.[9]	N/A	Level 2b	CRS + (HIPEC (86%) or EPIC (14%))	523	N/A
Glehen et al.[10]	1987–2002	Level 2b	CRS + HIPEC and/or EPIC	506	53
Gomez et al.[11]	1990–2004	Level 2b	CRS + HIPEC ± EPIC ± SC	266 (19%)	N/A
Sugarbaker et al.[12]	1982–1992	Level 2b	CRS + EPIC + SC in CRPC vs. appendiceal carcinomas	51	24
Sugarbaker et al.[13]	1982–1994	Level 2b	CRS + EPIC + SC	64	12
Pestieau et al.[14]	1981–1999	Level 2b	CRS ± HIPEC + EPIC (concomitant vs. delayed (complete vs. incomplete cytoreduction))	104 (5 vs. 44 vs. 55)	57 vs. 40 vs. 12
Carmignani et al.[15]	1992–2003	Level 2b	CRS ± HIPEC and/or EPIC + SC	27	18.5
Gomes da Silva et al.[16]	1981–2004	Level 2b	CRS + EPIC or HIPEC + SC	70	46.5
Beaujard et al.[17]	1991–1997	Level 2b	CRS + HIPEC ± SC	83 (33%)	N/A
Glehen et al.[18]	1989–2002	Level 2b	CRS + HIPEC + SC	53	59.5
Elias et al.[19]	1993–1999	Level 2b	CRS + EPIC vs. CRS + HIPEC	64 (86%)	51.7
Elias et al.[20]	1998–2001	Level 2b	CRS + HIPEC	24	27.4
Elias et al.[21]	1998–2003	Level 2b	CRS + HIPEC + SC	30	55
Elias et al.[22]	1999–2002	Level 2b	CRS + EPIC vs. CRS + HIPEC	23 vs. 23	113
Elias et al.[23]	2003–2005	Level 2b	CRS + HIPEC	106 (40%)	N/A
Witkamp et al.[24]	1995–1997	Level 2b	CRS + HIPEC ± SC	29 (90%)	38
Verwaal et al.[25]	1995–2002	Level 2b	CRS + HIPEC + SC	102 (85%)	41.6
Verwaal et al.[26]	1995–2003	Level 2b	CRS + HIPEC + SC	117	46
Loggie et al.[27]	1992–1997	Level 2b	CRS + HIPEC	84 (45%)	27.1
Shen et al.[28]	1991–1997	Level 2b	CRS + HIPEC ± SC	109 (37%)	52
Shen et al.[29]	1991–2002	Level 2b	CRS + HIPEC ± SC	77	15
Levine et al.[30]	1991–2006	Level 2b	CRS + HIPEC	460 (29%)	55.4
Shen et al.[31]	1992–2005	Level 2b	CRS + HIPEC ± EPIC	121	86
Cavaliere et al.[32]	1995–1998	Level 2b	CRS ± HIPEC ± EPIC ± SC	35 (31%)	17
Cavaliere et al.[33]	1995–1999	Level 2b	CRS + HIPEC or EPIC	40 (35%)	20
Cavaliere et al.[34]	1996–2005	Level 2b	CRS + HIPEC	120	N/A
Hadi et al.[35]	1996–2004	Level 2b	CRS ± HIPEC ± EPIC ± SC	60 (25%)	N/A
Yan et al.[36]	1997–2006	Level 2b	CRS + HIPEC + EPIC + SC	30	12
Yan et al.[37]	1997–2007	Level 2b	CRS + HIPEC	50	14
Schneebaum et al.[38]	1991–1996	Level 2b	CRS + HIPEC	15	10

TABLE 1 continued

Author and year	Study period	Evidence	Intervention	Study sample (CRC%)	Follow-up (months)
Pilati et al.[39]	1995–2001	Level 2b	CRS + HIPEC	46	14.5
Kecmanovic et al.[40]	1996–2003	Level 2b	CRS + HIPEC	18	21
Zanon et al.[41]	1998–2004	Level 2b	CRS + HIPEC	25	>36
Roviello et al.[42]	2000–2005	Level 2b	CRS + HIPEC	59 (32%)	25
Fuzun et al.[43]	1996–2005	Level 2b	CRS + NIC + EPIC	29	24
Kianmanesh et al.[44]	1996–2006	Level 2b	CRS + HIPEC ± SC	43	N/A
van Leeuwen et al.[45]	2003–2006	Level 2b	CRS + HIPEC	103 (37%)	13
Hansson et al.[46]	1991–2004	Level 2b	CRS + SPIC or HIPEC + EPIC	123 (48%)	36
Gusani et al.[47]	2002–2005	Level 2b	CRS + HIPEC	122 (25%)	35.6
Franko et al.[48]	2001–2007	Level 2b	CRS + HIPEC (MVR vs. control)	35 vs. 30	N/A
Ceelen et al.[49]	2005–2007	Level 2b	CRS + HIPEC	52 (63%)	14.4
Hagendoorn et al.[50]	2005–2008	Level 2b	CRS + HIPEC	49 (82%)	14
Akaishi et al.[51]	2002–2006	Level 2b	CRS + HIPEC	46 (28%)	N/A

NIC normothermic intraoperative chemotherapy, *SPIC* sequential intraperitoneal chemotherapy, *MVR* multivisceral resection

with peritoneal carcinomatosis, only 19% were of colorectal origin, and data should be interpreted with care.[11] A number of comparative studies were identified. Elias et al. conducted two comparative studies on CRS and HIPEC versus CRS and EPIC.[19,22] Other comparative studies focused on early versus late timing of cytoreduction, CRS and HIPEC performed with or without liver resection, and with or without multivisceral resection.[15,31,48]

The largest study included in this review was an unpublished multi-institutional study performed by Elias et al., involving 523 patients from 23 French institutions.[9] Eighty-six percent of these patients had CRS in combination with HIPEC, whilst 14% had CRS with EPIC. It should be noted that 85% of patients included in this study achieved complete cytoreduction. An earlier multi-institutional study on patients with CRPC was performed by Glehen et al., who included 506 patients from 28 international institutions during 1987–2002, with an average follow-up of 53 months.[10] The other multi-institutional study included in this systematic review was conducted by Gomez et al., who included 266 patients, only 19% of whom had CRPC.[11] Follow-up was not clearly documented in this study. Although median survival in all patients was recorded as 8.3 months, there was no yearly survival rate, and isolated survival data for patients with CRPC was not included. In addition, there was no documentation of chemotherapeutic regimens.

Forty single-institutional observational studies met the inclusion and exclusion criteria. These reports were conducted in tertiary referral centers. In all these studies, it should be noted that patient selection criteria differed between centers and individual trials, and patients with lymph node and/or liver metastasis were included in some trials whilst excluded in others. Similarly, the extent of intraperitoneal disease, measured by Peritoneal Cancer Index (PCI), also varied between studies. In addition, each treatment centre prescribed different regimens for PIC (drug, route, timing, dose, and duration) and varied in the amount of detail given in their papers (see Table 2). The most common regimens consisted of HIPEC with 40 mg mitomycin C (MMC) for 90–120 min at 42°C, followed by EPIC with 5-FU (650 mg/m^2) on POD 1–5 with or without MMC. Intravenous adjuvant chemotherapy was often utilized but generally not well documented. Follow-up ranged from 10 to 113 months.

Assessment of Survival

An overview of survival for patients with CRPC is presented in Table 3. Verwaal et al. randomized 105 patients into a standard arm ($n = 54$) with palliative surgery followed by systemic chemotherapy consisting of either LV (80 mg/m^2) and 5-FU (400 mg/m^2), or irinotecan

TABLE 2 Chemotherapy regimens for patients with colorectal peritoneal carcinomatosis (CRPC) undergoing hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), and intravenous chemotherapy

Study	Intraperitoneal chemotherapy regimen	Intravenous chemotherapy regimen
Verwaal et al.[5]	HIPEC: MMC (45 mg/m^2) for 90 min at 41–42°C	Standard arm and adjuvant chemotherapy: LV (80 mg/m^2) + 5-FU (400 mg/m^2) weekly for 26 weeks or irinotecan (350 mg/m^2) every 3 weeks for 6 months
Elias et al.[6]	EPIC: MMC on POD 1; 5-FU on POD 2–5	Preoperatively: 5-FU + LV for ≥ 3 months ± oxaliplatin ± irinotecan; Postoperatively: 5-FU + LV bimonthly for 6 months, starting 1 month after EPIC
Elias et al.[7]	HIPEC: oxaliplatin (460 mg/m^2) ± irinotecan for 30 min at 43°C	HIPEC group: 1 h prior to HIPEC: 5-FU (400 mg/m^2) + LV (20 mg/m^2); adjuvant chemotherapy: oxaliplatin ± irinotecan ± 5-FU or others Control group: oxaliplatin ± irinotecan ± 5-FU ± LV or others
Mahteme et al.[8]	EPIC: 5-FU (550 mg/m^2/day) on POD 1–6 at 4–6 weekly intervals for eight cycles; two patients had cisplatin and irinotecan	Adjuvant chemo: leucovorin (60 mg/m^2); Control group: 5-FU + LV ± methotrexate
Elias et al.[9]	Regimen unclear	Regimen unclear
Glehen et al.[10]	HIPEC: MMC ± cisplatin or oxaliplatin; EPIC: 5-FU ± MMC	204 patients had adjuvant chemotherapy: 5-FU ± LV ± cisplatin or oxaliplatin
Gomez et al.[11]	Regimen unclear	Regimen unclear
Sugarbaker et al.[12]	EPIC: MMC (10–12 mg/m^2) on POD 1 + 5-FU (15 mg/kg) on POD 2–5	MMC (10 mg/m^2) on third day of adjuvant chemotherapy
Sugarbaker et al.[13]	EPIC: MMC (10–12 mg/m^2) on POD 1; 5-FU (15 mg/kg) on POD2–5; 3–4 cycles	MMC
Pestieau et al.[14]	HIPEC: MMC; EPIC: 5-FU	None
Carmignani et al.[15]	HIPEC: MMC (10–12.5 mg/m^2) for 90 min at 42°C; EPIC: 650 mg/m^2 on POD 1–5; ten had HIPEC + EPIC; seven EPIC only	Data not collected
Gomes da Silva et al.[16]	First 36: EPIC: MMC (10–12.5 mg/m^2) on POD 1 + 5-FU (650 mg/m^2) on POD 2–6; weekly cycles for six cycles; Second 34: HIPEC: MMC (10–12.5 mg/m^2) for 90 min at 41–42°C + 5-FU (650 mg/m^2) on POD 1–5	Regimen unclear
Beaujard et al.[17]	HIPEC: MMC (10 mg/l) for 90 min at 46–49°C (inflow)	9 patients: 5-FU + folinate (6–12 courses) 1 month postoperatively
Glehen et al.[18]	HIPEC: MMC (40–60 mg) for 90 min at 46–48°C (inflow)	36 patients: 5-FU + oxaliplatin + irinotecan
Elias et al.[19]	HIPEC: MMC alone (5–10 mg/m^2 in 3.5 L/m^2) or at 20 mg/m^2 with cisplatin (200 mg/m^2 in 2.5 L/m^2) for 60 min at 41–44°C; EPIC: MMC (10 mg/m^2) on POD 1; 5-FU (500 mg/m^2) on POD 2–6	None
Elias et al.[20]	HIPEC: oxaliplatin	Regimen unclear
Elias et al.[21]	HIPEC: oxaliplatin (460 mg/m^2) for 30 min at 43°C	1 h prior to HIPEC: 5-FU (400 mg/m^2) and LV (20 mg/m^2)
Elias et al.[22]	HIPEC: oxaliplatin (460 mg/m^2) for 30 min at 42–44°C); EPIC: MMC (10 mg/m^2) on POD 0; 5-FU (650 mg/m^2) on POD 1–4	1 hour prior to HIPEC: LV (20 mg/m^2) + 5-FU (400 mg/m^2)
Elias et al.[23]	HIPEC: oxaliplatin (360 mg/m^2) + irinotecan (360 mg/m^2) for 30 min at 43°C	30 min prior to HIPEC: LV (20 mg/m^2) + 5-FU (400 mg/m^2)
Witkamp et al.[24]	HIPEC: MMC (15–40 mg/m^2) for 90 min at 41–42°C	5-FU (400 mg/m^2) + LV (80 mg/m^2) for 6 months, 6–12 weeks after discharge
Verwaal et al.[25]	HIPEC: MMC (15–35 mg/m^2) for 90 min at 41–42°C inflow	5-FU (400 mg/m^2) + LV(80 mg/m^2) weekly starting 6 weeks after HIPEC, for 26 weeks
Verwaal et al.[26]	HIPEC: MMC (35 mg/m^2) for 90 min at 40–41°C	5-FU (400 mg/m^2) + LV (80 mg/m^2) weekly for 6 months
Loggie et al.[27]	HIPEC: MMC (30–40 mg/m^2) for 90–120 min at 40.5°C	Regimen unclear
Shen et al.[28]	HIPEC: MMC (20–40 mg) for 120 min at 40.5°C (inflow)	Regimen unclear

TABLE 2 continued

Study	Intraperitoneal chemotherapy regimen	Intravenous chemotherapy regimen
Shen et al.[29]	HIPEC: MMC (30–40 mg) for 1–2 h at 39.5–40.5°C	Regimen unclear
Levine et al.[30]	HIPEC: MMC (40 mg) for 120 min at 40°C	Regimen unclear
Shen et al.[31]	Regimen unclear	41/121 received adjuvant chemotherapy; regimen unclear
Cavaliere et al.[32]	HIPEC: MMC (3.3 mg/m^2/l) + cisplatin (25 mg/m^2/l) at 41.5–42.5°C for 90 min; EPIC: 5-FU (13.5 mg/kg) + lederfolin (125 mg/m^2) on POD 1–5	Regimen unclear
Cavaliere et al.[33]	HIPEC: MMC (3.3 mg/m^2/l) + cisplatin (25 mg/m^2/l) at 41.5–42.5°C for 90 min; EPIC: 5-FU (13.5 mg/kg) + lederfolin (125 mg/m^2) on POD 1–5	Regimen unclear
Cavaliere et al.[34]	HIPEC: MMC (3.3 mg/m^2/l) + cisplatin (25 mg/m^2/l) at 41.5–43°C; 11 had oxaliplatin (360 mg/m^2) for 30 min at 43°C	Regimen unclear
Hadi et al.[35]	HIPEC: MMC (10–12.5 mg/m^2) for 90 min at 41–42°C; EPIC: 5-FU (650 mg/m^2/day) on POD 1–5 ± MMC on POD 1	Regimen unclear
Yan et al.[36]	HIPEC: MMC (10–12.5 mg/m^2) for 90 min at 42°C; EPIC: 5-FU (650 mg/m^2) on POD 1–5 or FUDR (2 patients only)	5-FU + LV
Yan et al.[37]	HIPEC: MMC (10–12.5 mg/m^2) for 90 min at 42°C; EPIC: 5-FU (650–800 mg/m^2) on POD 1–5 or FUDR (2 patients only)	Regimen unclear
Schneebaum et al.[38]	HIPEC: MMC (45–60 mg) for 60 min at 39–42°C	Preoperatively: All patients; postop.: unclear
Pilati et al.[39]	HIPEC: MMC (3.3 mg/m^2/l) + cisplatin (25 mg/m^2/l)	Preoperatively: none; Postoperatively: patients with recurrence of disease given 5-FU
Kecmanovic et al.[40]	HIPEC: MMC (10–12.5 mg/m^2) for 120 min at 42°C; EPIC: 5-FU (15 mg/kg) at 42°C on POD 1–5	None
Zanon et al.[41]	HIPEC: MMC (15 mg/m^2) for 60 min at 42°C	None
Roviello et al.[42]	HIPEC: oxaliplatin (460 mg/mq) or MMC (25 mg/mq) and cisplatinum (100 mg/mq) for 60 min at 41–43°C	None
Fuzun et al.[43]	Intraoperative non-heated chemotherapy: 5-FU (1,000 mg) for 20 min; EPIC: 5-FU (750 mg/m^2/day) on POD 1–5	5-FU for 6 months
Kianmanesh et al.[44]	HIPEC: MMC (120 mg in 6 L) + cisplatin (200 mg/m^2 in 6 L) for 90–120 min at 41–43°C	5-FU + oxaliplatin and/or irinotecan
van Leeuwen et al.[45]	HIPEC: oxaliplatin (460 mg/m^2); EPIC: 5-FU (550 mg/m^2/day) on POD 0–4	5-FU (500 mg/m^2) + Isovorin (30 mg/m^2); 2 patients: 5-FU + oxaliplatin, 1 patient: IFN + 5-FU
Hansson et al.[46]	HIPEC: oxaliplatin (460 mg/m^2); EPIC: 5-FU (550 mg/m^2/day) on POD 0–4; SPIC: 5-FU (550 mg/m^2/day) on POD 0–4	5-FU (500 mg/m^2) during HIPEC + LV (60 mg/m^2/day) on POD 0–4
Gusani et al.[47]	HIPEC: MMC (40 mg) for 100 min at 42°C	None
Franko et al.[48]	HIPEC: MMC (40 mg)	None
Ceelen et al.[49]	HIPEC: oxaliplatin (460 mg/m^2) for 30 min at 41–42°C	Immediately prior to HIPEC: Folate (20 mg/m^2) + 5-FU (400 mg/m^2)
Hagendoorn et al.[50]	HIPEC: MMC (35 mg/m^2) for 90 min at 40°C	None
Akaishi et al.[51]	HIPEC: MMC (35 mg/m^2) for 90 min or oxaliplatin (460 mg/m^2) for 30 min at 40°C	None

MMC mitomycin c, *POD* postoperative day, *5-FU* 5-fluorouracil, *LV* leucovorin, *IFN* interferon

(350 mg/m^2), and an experimental arm ($n = 51$), in which patients were treated by CRS and HIPEC (MMC 45 mg/m^2 for 90 min at 41–42°C), followed by the same systemic regimen.[5] The median survival was 12.6 months and the 2-year survival was 22% in the control arm. In comparison, the median survival was 22.3 months and the 2-year survival was 44% in the experimental arm ($P = 0.032$).

Elias et al. attempted to conduct an RCT in 1996, comparing CRS, EPIC, and systemic chemotherapy with CRS and systemic chemotherapy alone.[6] This study was abandoned prematurely, because only 35 patients were enrolled, short of the 90 patients required. Data from this incomplete RCT did not demonstrate any statistically significant advantage for the additional EPIC in survival. However, it was found that patients with complete cytoreduction achieved a 2-year survival of 60%, much higher than the expected 10% survival rate in patients with CRPC treated by the traditional regimen.

Another retrospective study by Elias et al. compared two groups of 48 patients who either had CRS, HIPEC, and systemic chemotherapy, or systemic chemotherapy alone.[7] Chemotherapeutic regimens for HIPEC included oxaliplatin (460 mg/m^2/day), given with or without irinotecan. Patients in the experimental group also received intravenous 5-FU (400 mg/m^2) and LV (20 mg/m^2) before and during CRS to potentiate oxaliplatin activity. Systemic chemotherapy in both groups included modern agents such as oxaliplatin and irinotecan, given in conjunction with 5-FU and a number of other agents. The median survival was 23.9 months and the 2-year survival was 65% in the control arm. In comparison, the median survival was 62.7 months and the 2-year survival was 81% in the experimental arm ($P < 0.05$).

Mahteme et al. recorded 18 patients who were treated by CRS with EPIC (5-FU 550 mg/m^2/day or cisplatin and irinotecan) and systemic chemotherapy (LV 60 mg/m^2), and compared them to matched patients in the control arm, who had palliative surgery and systemic chemotherapy (5-FU and LV with or without methotrexate).[8] The median survival, and 2- and 5-year survival rate were 14 months, 10%, and 5%, respectively, in the control arm. In comparison, the median survival, and 2- and 5-year survival rate were 32 months, 60%, and 28%, respectively, in the experimental group ($P = 0.01$).

The above four studies comparing combined therapy involving CRS and PIC with controls were subjected to meta-analysis. From the meta-analysis (Fig. 1), it can be seen that a significant improvement in survival was associated with treatment by CRS and HIPEC compared with palliative approach ($P < 0.0001$).[5] The pooled data from the comparative studies by Elias et al. and Mahteme and colleagues did not show a significant improvement in overall survival for patients treated by CRS, EPIC, and systemic chemotherapy versus surgery and systemic chemotherapy ($P = 0.35$).[7,8] The overall effect of PIC is significantly better than the control group ($P = 0.0002$). There was no heterogeneity ($I^2 = 1.6\%$) amongst all the studies.

In the multi-institutional study conducted by Elias et al., 1-, 3-, and 5-year survival rates of all patients were 81%, 41%, and 27%, respectively, with a median survival of 30 months and an average hospital stay of 22.5 days.[9] A subset of 416 patients (85%) who achieved complete cytoreduction had a 5-year survival of 30% and a median survival of 33 months. Overall perioperative morbidity and mortality rates were 30% and 3%, respectively.

In comparison, Glehen et al. recorded 1-, 3-, and 5-year survival rates of 72%, 39%, and 19%, respectively, with a median survival of 19.2 months.[10] Two hundred and seventy-one patients achieved complete cytoreduction (54%). Perioperative morbidity and mortality rates were 22.9% and 4%, respectively. Similar to Elias, completeness of cytoreduction was found to be the most important prognostic factor, with patients achieving complete cytoreduction having a median survival of 32.4 months, compared with 8.4 months for patients who failed to do so.

The other observational studies demonstrated that overall median survival varied greatly from 11.9 to 60.1 months.[12–51] The 1-, 2-, 3-, 4-, and 5-year survival rates from these studies had a median of 76%, 55%, 36%, 28%, and 19%.[12–51] Perioperative morbidity and mortality rate for all cytoreductive surgery procedures ranged from 14.8% to 76%, and 0% to 12%, respectively.[12–51] Average duration of hospital stay ranged from 9 to 29 days (Table 3).[12–51]

Assessment of Lymph Node Metastasis

Fourteen articles included in the present systematic review documented the presence of lymph node involvement, 11 of which stated a significant or nonsignificant effect on survival.[9–11,13,15,16,18,19,29,31] Of the 11 studies, 7 had shown a statistically nonsignificant effect on the prognosis.[11,13,15,16,19,29,31] The largest, and most recent of these studies, conducted by Shen et al., included 69 patients who were node negative with a median survival of 17.6 months (95% CI = 14.6–27.6 months), and 45 patients who were node positive with a median survival of 15.4 months (95% CI = 10.1–20.4 months; $P = 0.63$).[31] The other three studies, two of which were multi-institutional studies, found lymph node involvement to have a statistically significant negative prognostic effect on survival. One hundred and twenty-five patients were evaluated for their lymph node metastasis in the multi-institutional study conducted by Elias et al.[9] This revealed a statistically significant difference on both univariate and multivariate

TABLE 3 Survival, perioperative morbidity rates, mortality rates, and duration of hospital stay of patients with colorectal peritoneal carcinomatosis (CRPC) after cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC)

Study	1-Year survival	2-Year survival	3-Year survival	4-Year survival	5-Year survival	Median survival (months)	Mortality rate	Morbidity rate	Hospital stay (days)
Verwaal et al.[5]	56% vs. 67%	22% vs. 44%	N/A	N/A	N/A	12.6 vs. 22.4	N/A vs. 8%	N/A	HIPEC 29
Elias et al.[6]	80% vs. 89%	60% vs. 53%	45% vs. 30%	23% vs. 20%	20%	N/A	19% vs. 0%	50% vs. 37%	N/A
Elias et al.[7]	95% vs. 75%	81% vs. 65%	71% vs. 31%	54% vs. 20%	51% vs. 13%	62.7 vs. 23.9	N/A	N/A	N/A
Mahteme et al.[8]	71% vs. 44%	60% vs. 10%	32% vs. 5%	N/A	28% vs. 5%	32 vs. 14	0%	N/A	N/A
Elias et al.[9]	81%	57%	41%	33%	27%	30	3%	30%	22.5
Glehen et al.[10]	72%	44%	39%	24%	19%	19.2	4%	22.90%	N/A
Gomez et al.[11]	N/A	N/A	N/A	N/A	N/A	8.3	N/A	N/A	N/A
Sugarbaker et al.[12]	60%	40%	36%	N/A	N/A	N/A	N/A	N/A	N/A
Sugarbaker et al.[13]	N/A	N/A	N/A	N/A	N/A	11.9	N/A	23.20%	N/A
Pestieau et al.[14]	100% vs. 84% vs. 38%	100% vs. 54% vs. 14%	100% vs. 48% vs. 4%	100% vs. 35% vs. 4%	100% vs. 30% vs. 0%	N/A vs. 24 vs. 12	N/A	N/A	N/A
Carmignani et al.[15]	58%	25%	18%	17%	13%	15.2	0%	14.80%	N/A
Gomes da Silva et al.[16]	88%	N/A	44%	N/A	32%	33	N/A	N/A	N/A
Beaujard et al.[17]	N/A	N/A	N/A	N/A	N/A	12	N/A	N/A	N/A
Glehen et al.[18]	55%	32%	N/A	N/A	11%	12.8	4%	23%	14.8
Elias et al.[19]	85% vs. 83%	70% vs. 54%	54% vs. 44%	54% vs. 24%	44% vs. 17%	35.9	9.30%	54.60%	EPIC 25; HIPEC 30
Elias et al.[20]	83%	75%	65%	N/A	N/A	N/A	8%	N/A	N/A
Elias et al.[21]	97%	73%	53%	49%	48.50%	60.1	0%	40%	N/A
Elias et al.[22]	87% vs. 95%	56% vs. 78%	46% vs. 63%	33% vs. 54%	28% vs. 54%	N/A	8.7% vs. 0%	57% vs. 48%	N/A
Elias et al.[23]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Witkamp et al.[24]	82%	45%	23%	19%	N/A	N/A	3%	38%	23
Verwaal et al.[25]	71%	38%	27%	22%	N/A	19.9	N/A	N/A	N/A
Verwaal et al.[26]	75%	N/A	28%	N/A	19%	21.8	6%	N/A	N/A
Loggie et al.[27]	60%	39%	24%	16%	N/A	14.3	N/A	N/A	N/A
Shen et al.[28]	60.00%	N/A	24.60%	N/A	N/A	14.4	N/A	N/A	N/A
Shen et al.[29]	56%	N/A	25%	N/A	17%	16	12%	30%	10
Levine et al.[30]	N/A	N/A	N/A	N/A	N/A	16.4	N/A	N/A	N/A
Shen et al.[31]	91%	60%	48%	32%	26%	34	5.50%	42%	10
Cavaliere et al.[32]	N/A	54.70%	N/A	N/A	N/A	N/A	N/A	N/A	N/A

TABLE 3 continued

Study	1-Year survival	2-Year survival	3-Year survival	4-Year survival	5-Year survival	Median survival (months)	Mortality rate	Morbidity rate	Hospital stay (days)
Cavaliere et al.[33]	N/A	63.50%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cavaliere et al.[34]	N/A	N/A	25.80%	N/A	N/A	19	3.30%	22.5	N/A
Hadi et al.[35]	N/A	50%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yan et al.[36]	72%	64%	N/A	N/A	N/A	29	0%	N/A	27
Yan et al.[37]	79%	67%	39%	N/A	N/A	29	0%	76%	29
Schneebaum et al.[38]	N/A	N/A	N/A	N/A	N/A	N/A	0%	N/A	N/A
Pilati et al.[39]	68%	31%	N/A	N/A	N/A	18	0%	35%	11
Kecmanovic et al.[40]	86%	N/A	N/A	N/A	N/A	15	0%	44%	14.2
Zanon et al.[41]	64%	40%	N/A	N/A	N/A	30.3	4%	24%	N/A
Roviello et al.[42]	95%	74%	68%	54%	N/A	N/A	N/A	45%	N/A
Fuzun et al.[43]	72%	N/A	13%	N/A	7%	21	0%	41%	N/A
Kianmanesh et al.[44]	92%	72%	56%	44%	N/A	38.4	2%	39%	17
van Leeuwen et al.[45]	81%	63.70%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hansson et al.[46]	N/A	N/A	N/A	N/A	N/A	27	N/A	N/A	N/A
Gusani et al.[47]	76%	36.70%	36.70%	N/A	N/A	15.2	N/A	N/A	N/A
Franko et al.[48]	80% vs. 71%	46% vs. 30%	23% vs. 30%	16% vs. 30%	N/A	20.2 vs. 14.3	0% vs. 2.9%	63% vs. 56%	14.9 vs. 13.5
Ceelen et al.[49]	80%	N/A	N/A	N/A	N/A	N/A	0%	24%	19
Hagendoorn et al.[50]	88%	75%	N/A	N/A	N/A	N/A	0%	43%	12
Akaishi et al.[51]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

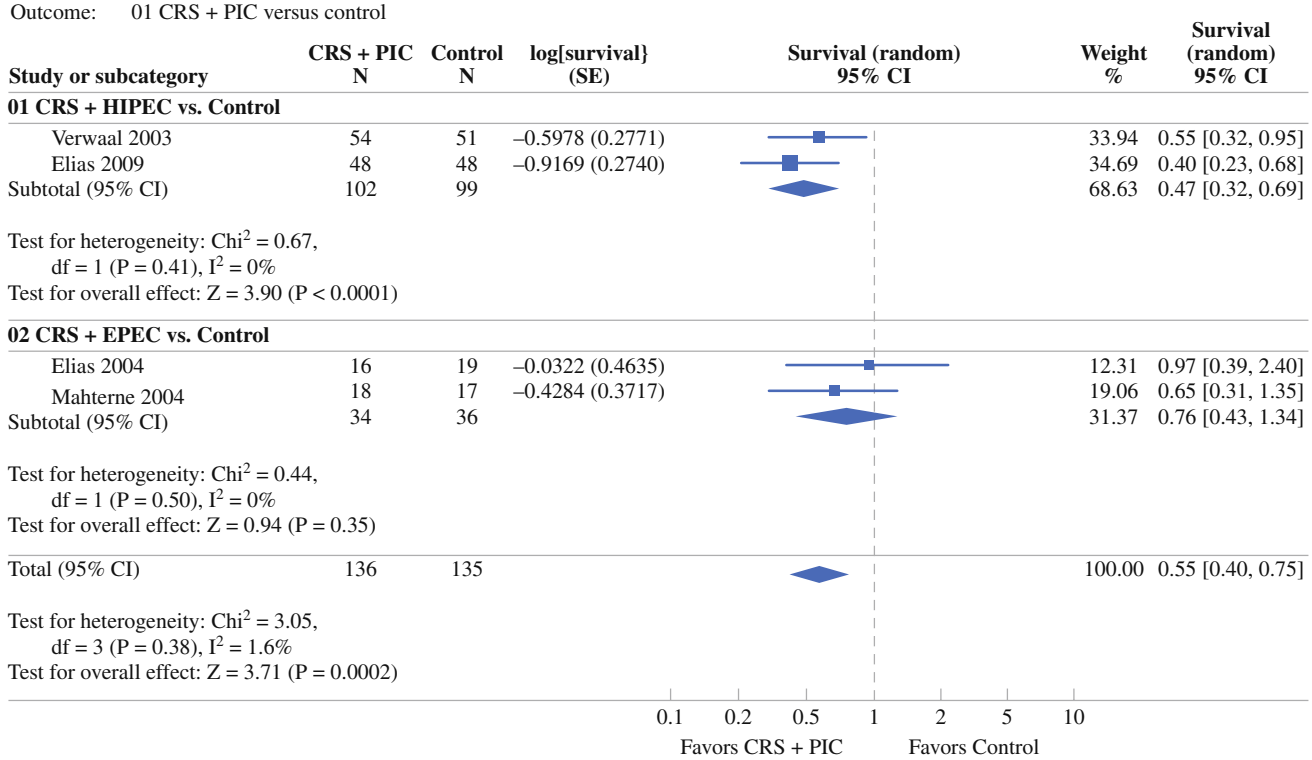

FIG. 1 Forest plot of the hazard ratio (HR) of the overall survival at three years with perioperative intraperitoneal chemotherapy (PIC) versus control for colorectal peritoneal carcinomatosis. The studies were analyzed according to the regimens of intraperitoneal chemotherapy used, i.e. hyperthermic intraperitoneal chemotherapy (HIPEC) or early postoperative intraperitoneal chemotherapy (EPIC). The estimate of the HR of each individual trial corresponds to the middle of the squares and horizontal line gives the 95% confidence interval (CI). For each subgroup, the sum of the statistics, along with the summary HR is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics

analysis between the node-positive and node-negative groups [$P = 0.02$, relative risk (RR) = 1.534]. Glehen et al. found 363 patients to be lymph node positive in their multi-institutional study, with a median survival of 18 months.[10] Comparatively, the 98 patients who did not have lymph node metastasis had a median survival of 31.2 months ($P = 0.003$).

Assessment of Liver Metastasis

Eleven studies in this systematic review documented the presence of liver metastasis.[9–11,13,15,20,22,29,31,36,44] One observational study by Shen et al. concluded that the presence of liver metastasis was statistically significant as a univariate predictor of survival, but this finding was lost on multivariate analysis.[29] Five studies stated liver metastasis had a statistically nonsignificant effect on the survival of patients with CRPC.[9,11,13,31,36] One of these was a multi-institutional study by Elias et al., who included 65 patients with documented liver metastasis, and compared them with patients who did not have liver metastasis.[9] The outcome for survival did not achieve statistical significance. It should be noted, however, that these five studies only included a selected group of patients that had liver metastasis deemed amendable to resection.

DISCUSSION

Peritoneal carcinomatosis is a malignancy of the peritoneal lining, which can be classified as either primary or secondary.[56,57] There are two ways in which secondary spread occurs. The first is by the tumor invading through the full-thickness bowel wall, as is often the case in colorectal carcinoma, or through the rupture of a noninvasive tumor, as is the case with mucinous epithelial tumors of the appendix, resulting in pseudomyxoma peritonei. Secondly, intraperitoneal spread may occur iatrogenically due to contamination of the surgical field and subsequent neoplastic emboli, either via hematogenous or lymphatic spread, or by direct seeding.[58] Until recently, CRPC has been considered a manifestation of systemic metastasis, and treated accordingly with systemic chemotherapy and palliative surgery. Jayne and co-workers reported that up to 58% of synchronous CRPC has been found to be confined

to the peritoneal cavity, and 64% of these patients had localized disease.[1] There is an evolving paradigm shift in the management of CRPC to achieve locoregional control, similar to hepatectomy for patients with isolated liver metastasis from colorectal carcinoma.

Traditional management of PC consisted of debulking or palliative surgery with or without systemic chemotherapy. Bypass, diversion, and resection procedures were usually performed to alleviate symptoms associated with complications.[59] The limited efficacy of systemic chemotherapy was shown in a prospective series of 100 patients with PC of nongynecological tumors, including 45 patients with CRPC. The majority of these CRC patients were treated with 5-florouracil (5-FU) and leucovorin (LV), and their median survival was 6 months.[2] Similarly, another prospective multicenter study by Sadeghi et al. involving 118 patients with CRPC resulted in a median survival of only 5.2 months.[3] Furthermore, a large retrospective study by Jayne et al. included 3,019 patients with colorectal cancer, 118 of whom had CRPC with a median survival of only 5.2 months.[1] Fifty-one patients in the control arm of the RCT conducted by Verwaal et al. achieved one of the better outcomes for survival, with a median survival of 12.6 months and 2-year survival of 22%.[5] More recently, Elias et al. reported a median survival of 23.9 months in a group of retrospectively selected patients who received modern systemic chemotherapeutic agents such as oxaliplatin and irinotecan in conjunction with 5-FU and others.[7] It should be noted that patients from the Verwaal[5] and Elias[7] studies had to be medically fit and negative from hematogenous metastasis to be included in the trials.[5,7]

CRS with PIC was advocated by Sugarbaker and colleagues in the 1990s as the definitive treatment for peritoneal dissemination from appendiceal adenocarcinomas. The aim of this combined treatment modality was to remove all macroscopic tumor nodules and any adhesions between the bowel loops, in order to allow chemotherapeutic agents to be uniformly distributed within the peritoneal cavity to eradicate any microscopic tumor deposits. The potential advantages of using HIPEC compared with intravenous chemotherapy included an increased exposure of chemotherapeutic drugs to the malignant cells of the peritoneum, an increase of drug penetration into the tissues, a synergistic effect with chemotherapy, and an independent cytotoxic effect of the hyperthermia.[60,61]

Over the last decade, a number of single-institutional studies have demonstrated an improved outcome using the combined treatment compared with survival rates from historic controls. Even though there has only been one completed RCT to date, the difficulty to perform such trials should not constitute a plea against randomization in the future. In addition, it should be noted that no RCTs demonstrated the superiority of hepatectomy over systemic chemotherapy for colorectal liver metastasis and no RCTs were ever conducted for liver transplant surgery. However, both of these procedures are currently accepted as the standard of care.

Although the current data on CRS and PIC are encouraging, widespread practice of this procedure should be sought with caution. Firstly, it should be noted that the characteristics of individual patients differed across treatment centers and individual trials. Exclusion criteria differed in age limitations, involvement of liver and lymph node metastasis, American Society of Anesthesiologists (ASA) grades, and other specific markers such as liver function tests and creatinine clearance. Generally, patients with poor performance status have been excluded from clinical trials and it is recognized that combined treatment is only appropriate for selected patients with CRPC. Secondly, benefits of the combined treatment should be considered with its associated morbidity and mortality. Specific morbidities are difficult to summarize due to scarcity of data for individual patient adverse outcomes. Perioperative morbidity ranged from 14.8% to 57%, but grading of morbidities varied in detail between studies.[5–51] Mortality rates ranged from 0% to 12%, with two large multi-institutional studies by Elias et al. and Glehen et al. reporting 3% and 4%, respectively.[5–51] In addition, all studies included in this review were conducted in tertiary referral centers with a special interest in peritonectomy procedures, and there appears to be a significant learning curve with performing these complex procedures.[30,62]

Progression of CRPC to involve lymph nodes has long been considered a significant prognostic factor.[14] Hence, the presence of lymph node metastasis has often been used as selection criterion for patients undergoing peritonectomy in some centres.[6,22] From this systematic review, it was found that seven individual studies failed to find a statistically significant effect of lymph node involvement.[11,13,15,18,19,29,31] However, two multi-institutional studies stated a statistically significant detrimental effect on survival.[9,10] This discrepancy could be due to the limited number of patients in smaller individual studies to show any statistical significance. Previous reports have suggested limited survival benefit for performing resection of liver metastases in the presence of CRPC.[63] This theory was echoed by Glehen et al., who concluded that synchronous resection of liver metastasis at the time of CRS was a statistically significant prognostic factor with a worse outcome in both univariate and multivariate analysis.[10] However, this was disputed by Carmignani et al. and Kianmanesh et al., who advocated liver resection for selected patients requiring minor operations, with the aim of complete removal of disease from the peritoneal cavity, liver, and other sites.[15,44] Their studies did not show any

statistical significance in performing synchronous hepatic metastatic resections.

The meta-analysis showed that combined therapy involving cytoreductive surgery and perioperative intraperitoneal chemotherapy had a statistically significant survival benefit over control groups. In the present systematic review, 2 RCTs, 2 controlled observational studies, 3 multi-institutional studies, and 40 case-series studies were examined. The current literature suggests that patients with liver metastasis amendable to resection should not be excluded from CRS and PIC. However, there is a need for further evaluation of the prognostic significance of lymph node and liver involvement, ideally in large prospective trials.

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