REVIEW

Summary of Current Therapeutic Options for Peritoneal Metastases From Colorectal Cancer

TERENCE C. CHUA, BscMed (Hons), MBBS,[1,2] JESUS ESQUIVEL, MD,[2]
JOERG O.W. PELZ, MD,[3] AND DAVID L. MORRIS, MD, PhD[1]*

[1]Hepatobiliary and Surgical Oncology Unit, Department of Surgery, University of New South Wales, St George Hospital, Sydney, Australia
[2]Department of Surgical Oncology, St Agnes Hospital, Baltimore, Maryland
[3]Department of Surgery, University of Wuerzburg, Wuerzburg, Germany

Background: Peritoneal metastases remain an under addressed problem for which this review serves to investigate the efficacy of systemic chemotherapy and radical surgical treatments in this disease entity.
Methods: The literature between 1995 and June 2009 was surveyed systematically through a review of published studies on the treatment outcomes of metastatic colorectal cancer to the peritoneum on the Medline and PubMed databases.
Results: A total of 2,492 patients from 19 studies were reviewed. One thousand and eighty-four patients treated with complete cytoreductive surgery (CCS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and 1,408 patients were treated with palliative surgery and/or systemic chemotherapy. For CCS HIPEC, the overall survival ranged between 20 and 63 (median 33) months, and 5-year survival ranged between 17% and 51% (median 40%). For palliative surgery and/or systemic chemotherapy, the overall survival ranged between 5 and 24 (median 12.5) months, and 5-year survival ranged between 13% and 22% (median 13%).
Conclusion: Systemic therapies have not proved effective and randomised clinical trials have not sufficiently addressed patient subpopulations with metastatic disease of this entity. Current evidence have demonstrated the efficacy associated with CCS HIPEC for which should now be embraced as the standard of care.
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KEY WORDS: **systemic chemotherapy; fluorouracil; Bevacizumab; Oxaliplatin; Cetuximab; Irinotecan; colorectal cancer; peritoneal carcinomatosis; metastasis**

INTRODUCTION

It is estimated that about 40% of patients with colorectal cancer will develop peritoneal metastases at some point in time after initial diagnosis [1]. This clinical manifestation is universally referred to with varying terminologies that include peritoneal metastases, peritoneal carcinomatosis, or diffuse intraabdominal metastases. Peritoneal metastases may occur as an isolated or combined site of treatment failure following initial curative surgery. By and large, peritoneal carcinomatosis is the dominant factor of patients' symptomatology where malignant bowel obstruction and ascites leads to profound anorexia and pain. Necropsies studies have shown that majority of patients dying of colorectal cancer have evidence of peritoneal metastases [2–4].

The occurrence of peritoneal metastases is a result of the growth of tumour that invades through the serosal lining of the bowel lumen allowing the exfoliation and shedding of malignant cells intraperitoneally. Iatrogenic manipulation during the surgical procedure such as transection of lymphatics or blood vessels may also lead to seeding of tumour cells within the peritoneal cavity hence contributing towards the etiological origins of this clinical entity [1,5]. As described in the seed and soil hypothesis of cancer invasion and metastasis [6,7], the implantation and establishment of a metastatic niche in the peritoneum is likely to be a result of various genes and proteins that characterise the intrinsic properties of these specific cancer cell [8], and the cancer cell–microenvironment interaction that have the propensity towards developing peritoneal metastasis [9–11]. Favoured sites of the peritoneal cavity include the subphrenic region, lesser sac, bowel surfaces and mesentery, and in the pelvis due to the direction of peritoneal fluid circulation and the effects of gravitational forces.

In the last decade, tremendous progress has been made in the medical management of metastatic colorectal cancer. The addition of Oxaliplatin and Irinotecan to previously existing 5-flurouracil (5-FU) and leucovorin-based therapies has improved the overall median survival that previously rarely exceeded 12 months [12]. Coupled with the addition of biological targeted therapies including Bevacizumab and Cetuximab, the overall median survival is now up to 20 months [13–18]. In addition, there are increasing evidence suggesting that radical surgery of metastases from colorectal cancer to sites such as the liver, lung, and peritoneum is associated with improved survival and possibly cure [19–22]. It is therefore of foremost interest that we present a review of the current medical and surgical therapies for

*Correspondence to: David L. Morris, MD, PhD, Professor, Department of Surgery, St George Hospital, University of New South Wales, Kogarah, NSW 2217 Sydney, Australia. Fax: +61-2-9113-3997.
E-mail: david.morris@unsw.edu.au

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peritoneal metastases from colorectal cancer based on the available evidence in the literature to elucidate the optimal management of this dire condition to determine an evidence-based practice for this clinical condition.

METHODS

Literature Search

The endpoint of this review was to determine whether intent to treat based on two treatment strategies of (1) radical surgery and intraperitoneal chemotherapy using the technique of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) or (2) palliative surgery and/or systemic chemotherapy on the survival outcomes of patients with peritoneal metastases from colorectal cancer. In patients undergoing cytoreductive surgery and HIPEC, those whereby a complete cytoreduction could not be achieved (incomplete cytoreduction) and undergoing HIPEC were also reviewed to determine the outcomes following failure of intended cytoreductive surgery and HIPEC. This was achieved through searching the MEDLINE and PubMed databases (1995 to June 2009) using the key words: 'Colorectal Cancer', 'Peritoneal' and 'Chemotherapy'. The reference lists of all retrieved articles were manually reviewed to further identify potentially relevant studies.

Selection Criteria

Publications where the treatment outcomes of patients with peritoneal metastases from colorectal cancer were reported were identified for inclusion. As not all patients undergoing cytoreductive surgery will attain a complete cytoreduction (CCS), a second group of patients who undergone cytoreductive surgery but had incomplete cytoreduction was created. Therefore the treatments were classified according to whether the reported treatment strategy was (1) CCS and HIPEC, (2) incomplete CS with or without intraperitoneal chemotherapy, or (3) palliative surgery and/or systemic chemotherapy. CS consisted of peritonectomy procedures (anterior parietal peritonectomy, omentectomy $\pm$ splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, and lesser omentectomy with stripping of the omental bursa $\pm$ cholecystectomy) and visceral resections (rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy, and small bowel resection) [23]. The type and extent of peritonectomy procedures were not uniformly performed in all the studies included, however, the survival of patients with residual tumour implants less than 2.5 mm were classified as a CCS (CC0/1). Resection where tumour implants $>$2.5 mm remained after CRS was classified as incomplete cytoreduction. HIPEC administration occurred intraoperatively after CS. Palliative surgery is an incomplete surgical procedure where there are macroscopically visible remnant tumours after surgery and is performed without a curative intent. This treatment is often combined with adjuvant systemic chemotherapy that would include conventional chemotherapy agents such as 5-flurouracil, Leucovorin, with or without other modern agent systemic agents including Oxaliplatin, Irinotecan, and targeted therapies including Bevacizumab, Cetuximab, and Pannitumumab.

Specific inclusion criteria were studies published after year 1995, with $\geq$30 patients for those treated with CS and HIPEC and $\geq$10 for those treated with palliative surgery and/or systemic chemotherapy, human articles and papers published in the English language. Abstracts, letters, editorials, and expert opinions were excluded. Studies reporting the treatment outcomes of patients with peritoneal carcinomatosis without specifically identifying the primary tumour origin or reporting survival results based on the type of primary tumour were excluded. All relevant articles identified were assessed with application of a predetermined selection criterion. Where multiple publications from the same institution were identified, only the most recent update with the largest number of patients or longer follow-up group was included. Multi-institutional studies were not excluded.

Data Extraction and Critical Appraisal

Studies were appraised using a standard protocol. Discrepancies were discussed and resolved by consensus. Data extracted included the treatment strategy and survival outcomes. This was performed through extracting information from article texts, tables, and figures. Studies were selected for evaluation if they were level I evidence: randomised controlled trials (RCTs); level II evidence: non-randomised controlled clinical trials or well-designed cohort studies; level III evidence: observational studies, as described by the U.S. Preventive Services Task Force.

RESULTS

Quantity and Quality of Evidence

Literature search using the above described search strategy through both MEDLINE and PubMed databases identified 279 studies. After selecting for only human and English articles, 211 studies remained. When the time period of after year 1995 to June 2009 was applied, 188 articles remained. From these 188 articles, the abstracts of original articles were reviewed with careful attention being paid to the inclusion criteria. Through this examination, 9 of 41 studies reporting outcomes of CS and HIPEC were selected for inclusion and the majority of excluded studies were due to not fulfilling the minimum patient number per published report. For studies reporting outcomes of palliative surgery and/or systemic chemotherapy, 11 of 40 studies were selected for inclusion with the majority being excluded due to not fulfilling the endpoints of survival from evaluation of a specific chemotherapy treatment was undertaken (Fig. 1).

These 18 studies were individually reviewed through careful analysis of the study methodology with reference to fulfilment of the systematic review's objective of elucidating the survival outcome of each treatment strategy for peritoneal metastases from colorectal cancer. There were two phase III randomised control trial (level I evidence), two phase II studies (level II evidence), and 14 observational studies (level III evidence). As this review reported only treatment with no comparisons, and there are varying heterogeneity of the methodology and specific treatment policies in each of the reviewed study, meta-analysis was not appropriate. The results were extracted and tabulated to report the survival outcomes through a narrative review with full tabulation of results of all included studies (Table I).

Patient and Treatment Characteristics

A total of 2,492 patients from 18 studies were reviewed [24–42]. One thousand and eighty-four patients reviewed underwent treatment of peritoneal metastases from colorectal cancer by CS and HIPEC. These studies were reported from countries in North America, Europe, and Australia between years 2003 and 2009 [24,27,29–31,36,40–42]. Eight of nine (88%) of studies reported the use of Mitomycin C as the agent in HIPEC [24,27,30,31,36,40–42]. Six of nine (67%) studies documented administration of adjuvant systemic chemotherapy after CS and HIPEC using 5-FU and Leucovorin [29–31,36,41,42]. Amongst these five studies, four had combined 5-FU and Leucovorin with modern agents that include Oxaliplatin, Irinotecan and Bevacizumab [29–31,36,42].

One thousand four hundred and eight patients reviewed underwent palliative surgery and/or systemic chemotherapy. These studies

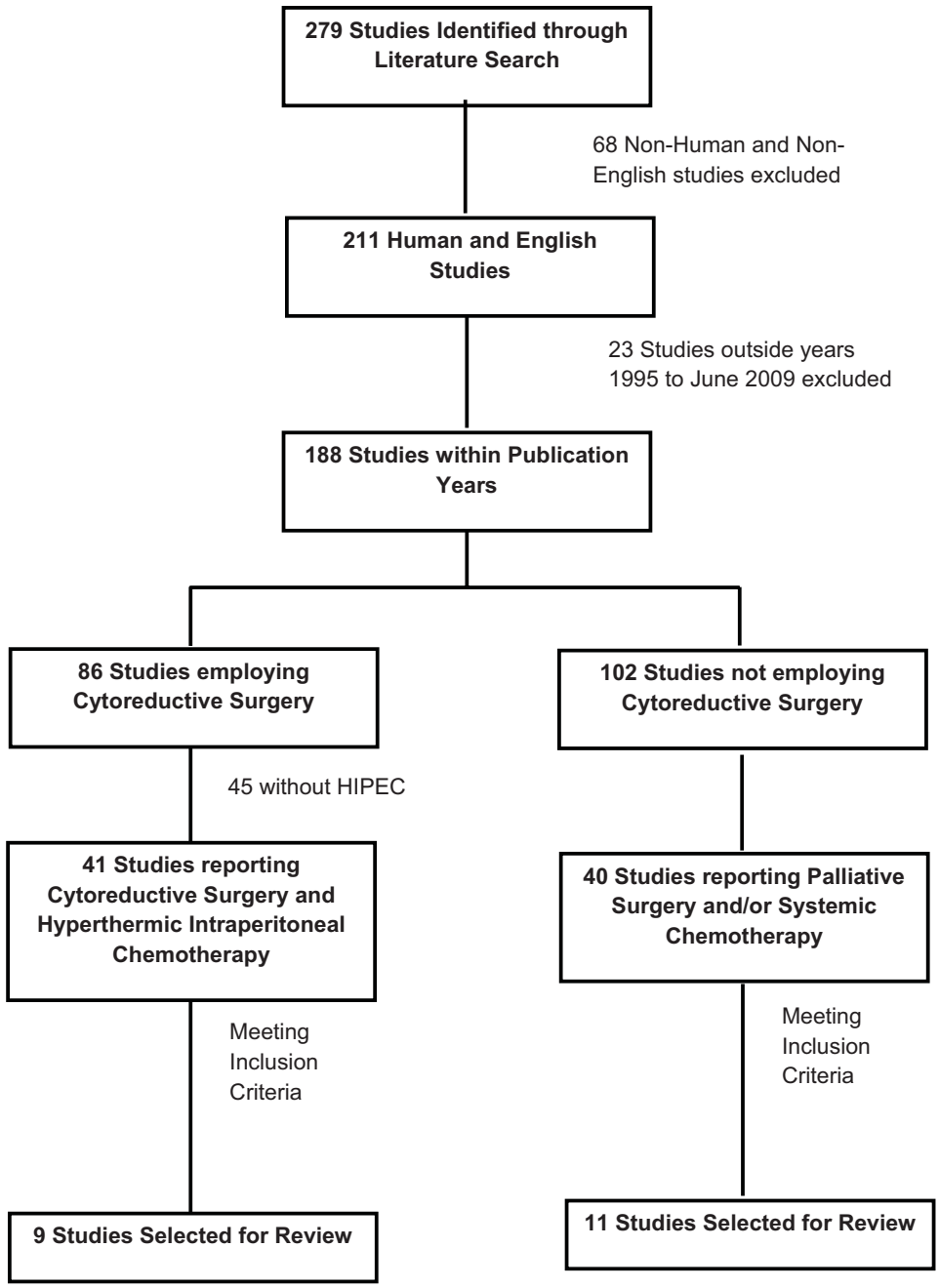

Fig. 1. Flowchart of publication identification and quality appraisal.

were reported from countries in Asia and Europe between years 2000 and 2009 [25,26,28,29,33–35,37–39,41]. All but one study specified performance of palliative surgical procedures in patients. One study did not specify any type of surgical procedure performed and was a pooled analysis from clinical trials [37]. Nine of 11 (82%) reported using systemic chemotherapy as part of treatment [25,26,28,29,33,34,37,38,41]. The agents administered were 5-FU and Leucovorin in 10 studies of which three had added modern agents [25,26,29]. One study specified the use of chemotherapy, however, did not mention the type of agents used [34] (Tables I and II).

Results of Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

In total, 663 patients from nine studies reported outcomes of CCS and HIPEC [24,27,29–31,36,40–42]. Only one study evaluated disease-free survival which was reported to be 9 months [24]. The median overall survival ranged between 20 and 63 months, with a median of 33 months [24,27,29–31,36,40,42]. The 3- and 5-year survival ranged between 44% and 56% (median 50%), and 20% and 51% (median 43%) respectively [24,27,29–31,36,40,42] (Table III).

TABLE I. Characteristics of the Studies Reviewed Divided Into the Type of Treatment Adopted for Peritoneal Metastases From Colorectal Cancer

Refs.	Institution	City	Year	Level of evidence	Total patients (n)
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy					
Chua et al. [27]	St George Hospital	Sydney	2009	III	60
Elias et al. [29]	Institut Gustave Roussy	Villejuif	2009	II	48
Shen et al. [40]	Wake Forest University	Winston-Salem	2008	III	121
Franko et al. [30]	University of Pittsburgh Medical Center	Pittsburgh	2008	III	65
Bijelic et al. [24]	Washington Cancer Institute	Washington DC	2008	III	70
Kianmanesh et al. [36]	Louis-Mourier University Hospital	Paris	2007	III	43
Verwaal et al. [42]	Netherlands Cancer Institute	Amsterdam	2005	III	117
Glehen et al. [31]	Multi-institutional	2004	III	506	
Verwaal et al. [41]	Netherlands Cancer Institute	Amsterdam	2003	I	54
Total	—	—	—	—	1084
Palliative surgery and/or systemic chemotherapy					
Catalano et al. [26]	Multi-institutional		2009	III	43
Elias et al. [29]	Institut Gustave Roussy	Villejuif	2009	II	48
Machida et al. [38]	Shizuoka Cancer Center	Shizuoka	2008	III	20
Hasegawa et al. [33]	Tokai University	Tokyo	2006	III	125
Bloemendaal et al. [25]	Netherlands Cancer Institute	Amsterdam	2005	III	50
Elias et al. [28]	Institut Gustave Roussy	Villejuif	2004	I	19
Higashi et al. [34]	Tokyo Kosei Nenkin Hospital	Tokyo	2003	III	21
Verwaal et al. [41]	Netherlands Cancer Institute	Amsterdam	2003	I	51
Kohne et al. [37]	Multi-institutional		2002	III	660
Jayne et al. [35]	Singapore General Hospital	Singapore	2002	III	253
Sadeghi et al. [39]	Multi-institutional		2000	II	118
Total	—	—	—	—	1408

Results of Incomplete Cytoreduction

From the CS HIPEC studies, 284 patients from seven studies reported patients with incomplete cytoreduction [27,30,31,36,40–42]. The median overall survival ranged from 8 to 17 months, with a median of 8 months [27,30,31,36,40–42]. The 1-, 2- and 3-year survival ranged from 15% to 67% (median 51%), 0–25% (median 5%), and 0–9% (median 0%), respectively [27,30,31,36,40–42].

Results of Palliative Surgery and/or Systemic Chemotherapy

Studies investigating the outcome of palliative surgery and/or systemic chemotherapy demonstrated a median overall survival ranging between 5 and 24 months, with a median of 12.5 months [25,26,29,33–35,37–39,41]. The 3- and 5-year survival ranged between 13% and 19% (median 16%), and 13% and 22% (median

TABLE II. Details of the Treatment Regime, in Particular the Intraperitoneal Chemotherapy Regimen Adopted

Refs.	Cytoreductive surgery (CRS)	Hyperthermic intraperitoneal chemotherapy (HIPEC)	Palliative surgery	Systemic chemotherapy
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy				
Chua et al. [27]	Yes	Mitomycin C	No	No
Elias et al. [29]	Yes	Oxaliplatin	No	5-FU, Leucovorin, Oxaliplatin, Irinotecan
Shen et al. [40]	Yes	Mitomycin C	No	No
Franko et al. [30]	Yes	Mitomycin C	No	5-FU, Leucovorin, Oxaliplatin, Irinotecan, Bevacizumab
Bijelic et al. [24]	Yes	Mitomycin C	No	No
Kianmanesh et al. [36]	Yes	Mitomycin C	No	5-FU, Leucovorin, Oxaliplatin, Irinotecan
Verwaal et al. [42]	Yes	Mitomycin C	No	5-FU, Leucovorin, Irinotecan
Glehen et al. [31]	Yes	Mitomycin C/Mitomycin C and Cisplatin/Oxaliplatin/Others	No	5-FU, Leucovorin, Oxaliplatin, Irinotecan
Verwaal et al. [41]	Yes	Mitomycin C	No	5-FU, Leucovorin
Palliative surgery and/or systemic chemotherapy				
Catalano et al. [26]	No	No	Yes	5-FU, Leucovorin, Oxaliplatin, Irinotecan
Elias et al. [29]	No	No	Yes	5-FU, Leucovorin, Oxaliplatin, Irinotecan
Machida et al. [38]	No	No	Yes	5-FU, Leucovorin
Hasegawa et al. [33]	No	No	Yes	5-FU, Leucovorin
Bloemendaal et al. [25]	No	No	Yes	5-FU, Leucovorin, Irinotecan
Elias et al. [28]	Yes	No	Yes	5-FU, Leucovorin
Higashi et al. [34]	No	No	Yes	Yes (Type NR)
Verwaal et al. [41]	No	No	Yes	5-FU, Leucovorin
Kohne et al. [37]	No	No	NR	5-FU, Leucovorin
Jayne et al. [35]	No	No	Yes	NR
Sadeghi et al. [39]	No	No	Yes	NR

TABLE III. Survival Outcomes of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy and Palliative Surgery and/or Systemic Chemotherapy for Peritoneal Metastases From Colorectal Cancer

Refs.	Patients (n)	Disease-free survival (months)	Overall survival (months)	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy							
Chua et al. [27]	54	NR	33	87	70	44	NR
Elias et al. [29]	48	NR	63	NR	81	NR	51
Shen et al. [40]	30	NR	41	NR	NR	NR	NR
Franko et al. [30]	36	NR	20	85	NR	45	NR
Bijelic et al. [24]	49	9	33	NR	NR	50	20
Kianmanesh et al. [36]	30	NR	38	NR	72	NR	44
Verwaal et al. [42]	59	NR	43	94	NR	56	43
Glehen et al. [31]	377	NR	32	90	NR	55	40
Verwaal et al. [41]	39	NR	22	70	45	NR	NR
Median		n/a	33	87	71	50	43
Range		n/a	20–63	70–94	45–81	44–56	20–51
Incomplete cytoreduction							
Chua et al. [27]	6	NR	14	67	25	0	0
Shen et al. [40]	36	NR	4	NR	NR	NR	NR
Franko et al. [30]	32	NR	8	15	0	0	0
Kianmanesh et al. [36]	13	NR	13	62	0	0	0
Verwaal et al. [42]	58	NR	17	66	NR	9	0
Glehen et al. [31]	129	NR	8	40	10	8	0
Verwaal et al. [41]	10	NR	6	25	NR	NR	NR
Median		n/a	8	51	5	0	0
Range		n/a	4–17	15–67	0–25	0–9	0
Palliative surgery and/or systemic chemotherapy							
Catalano et al. [26]	43	NR	11	NR	NR	NR	NR
Elias et al. [29]	48	NR	24	NR	65	NR	13
Machida et al. [38]	20	NR	12	NR	NR	NR	NR
Hasegawa et al. [33]	125	NR	15	67	25	13	13
Bloemendaal et al. [25]	50	8	13	55	25	19	NR
Elias et al. [28]	19	NR	NR	NR	60	NR	22
Higashi et al. [34]	21	NR	19	NR	NR	NR	NR
Verwaal et al. [41]	51	8	13	50	25	NR	NR
Kohne et al. [37]	660	NR	12	NR	NR	NR	NR
Jayne et al. [35]	253	NR	7	NR	NR	NR	NR
Sadeghi et al. [39]	118	NR	5	NR	NR	NR	NR
Median		n/a	12.5	55	25	16	13
Range		n/a	5–24	50–67	25–65	13–19	13–22

13%), respectively [25,28,33]. Only two studies reported data on disease-free survival, both of which report a median disease-free survival of 8 months [25,41] (Table III).

DISCUSSION

To our knowledge, this is the first comprehensive review that thoroughly addresses the treatment of the distinct entity of peritoneal metastases from metastatic colorectal cancer by documenting the various treatment options and outcomes. The authors also thoroughly searched through randomised trials of treatments for metastatic colorectal cancer within the last 10 years for where significant progress in systemic therapies has been made in chemotherapy treatment. However, none of the trials on systemic therapies have reported the peritoneum as a site of metastasis in patients entered into the trials. It is likely that selecting patients with peritoneal metastases for entry into such trials is not be possible due to the inability to obtain any baseline tumour size measurements on conventional computed tomography imaging scans, magnetic resonance imaging, and X-ray. This highlights the difficulties of applying the RECIST criteria [43] to examine the tumour response and efficacy of systemic treatments. For example, in the trial that led towards Bevacizumab becoming standard of care when used in combination with IFL regimen for patients with metastatic colorectal cancer [13], patients were required to have bi-dimensionally measurable disease and if malignant ascites was present, patients were excluded. An exclusion criteria as such would clearly fail to capture the pool of patients with peritoneal metastases. Therefore it is foreseeable that the majority of pharmacotherapeutic clinical trials would not have included patients with peritoneal metastases. Hence, we do not have evidence-based knowledge about the response and outcome of systemic treatments in this distinct subgroup of patients.

From long-term experience of managing patients with peritoneal metastases, this group of patients have been observed to often be the ones with the poorest response to systemic chemotherapy. This is supported by the survival outcomes of 1,408 patients from 11 studies that have been extracted through this review. Despite performing palliative resections, bypass procedures, administration of systemic chemotherapy using 5-FU and Leucovorin chemotherapy, the median overall survival ranges between 5 and 24 months (median 12.5 months). The study that reported the longest median survival time of 24 months after palliative surgery and systemic chemotherapy was by Elias et al. [29]. These authors reported a defined population of patients with limited isolated peritoneal metastases, the majority of which have well-differentiated tumours, and excluded patients that progressed rapidly on systemic treatment. Clearly, this self-selected population represent a group of patients with reasonably minimal peritoneal metastases for which treatment using modern agents such as Oxaliplatin and Irinotecan into the chemotherapy regimen might have explained the long survival outcome. A more representative

population that did not undergo such stringent selection for inclusion was the study reported by Catalano et al. [26]. In their study of predictors for poor response and overall survival in patients with colorectal cancer treated with first-line Oxaliplatin and/or Irinotecan-based chemotherapy, patients with peritoneal metastases were found to be associated with a poor overall survival on multivariate analysis, with a median overall survival of 11 months. In the largest reviewed study, Kohne et al. [37] performed a multivariate analysis of 3825 patients with metastatic colorectal cancer treated with 5-FU to determine predictive factors for survival. The patient cohort in this study was obtained from 19 prospective randomised and three phase II trials. Similar to the previous study by Catalano et al. [26], this study likewise identified patients with peritoneal metastases to predict for a worse outcome, with a median survival of 12 months.

In the last 5 years, the development of treatment of peritoneal metastases from various gastrointestinal and gynaecological cancers has rapidly evolved from a palliative approach towards a comprehensive management strategy using cytoreductive surgery and perioperative intraperitoneal chemotherapy [44]. This involves selecting patients with peritoneal metastases for radical surgical excision of peritoneal lesions combined with intraperitoneal chemotherapy delivered intraoperatively using a heated chemoperfusate. At times, during the immediate postoperative period, further intraperitoneal chemotherapy may also be delivered to attempt to destroy residual microscopic tumour cells. As shown in our review, centres adopting the management strategy of CCS and HIPEC who have reported their experience of treating $\geq$40 patients have demonstrated a median overall survival ranging between 20 and 63 months. Five-year survival is also a reality in approximately 20–51% of patients undergoing this radical surgical treatment. Worth emphasizing also is that in these centres, patients who fail to undergo a complete cytoreduction, be it due to the extensiveness of peritoneal implants or the lack of technical skills, the survival outcome is dismal with a median overall survival of 8 months with majority of patients succumbing to disease within a year. This is similar to the survival outcomes of the group of patients who underwent palliative surgery and/or systemic chemotherapy.

Despite the convincing superiority of the results of CCS and HIPEC as treatment for peritoneal metastases from colorectal cancer, there remains some scepticism with regards to the applicability, safety and efficacy of this treatment. There has been over a decade of animal experimentations, pharmacokinetic studies and surgical training of peritonectomy procedures to perform cytoreductive surgery that has formed the basic foundation and development of this treatment strategy [23,45–47]. There are today numerous tertiary treatment centres in every continent around the world offering this specialised treatment. In a recent meta-analysis to analyse the survival outcomes of patients with colorectal peritoneal metastases treated with CS and perioperative intraperitoneal chemotherapy, significant improvement in survival was associated with treatment by CS and HIPEC compared with palliative approach ($P < 0.0001$) through combining two studies that were included in this review [29,41,48] (Fig. 2). Importantly, the results from centres reviewed have reported encouraging long-term survival results. In terms of safety, a recent narrative systematic review of the morbidity and mortality of 24 treatment centres, of which 10 centres that were regarded as high volume specialised centres based on the number of procedures performed, showed a major morbidity rate ranging from 12% to 52% and a mortality rate ranging from 0.9% to 5.8% for which is considered acceptable given the magnitude of the surgical procedure involved [49]. The maturation of this treatment strategy involves gaining of experience and mastery of the surgical procedure and decision-making skills to select appropriate patients. This necessitates a learning curve for which the successful acquisition of the technicalities will translate to improve delivery of this treatment [50].

Hepatic resection for colorectal liver metastases has evolved since the early 1980s. It is now regarded as the standard of care for patients with resectable colorectal liver metastases [51]. Combining

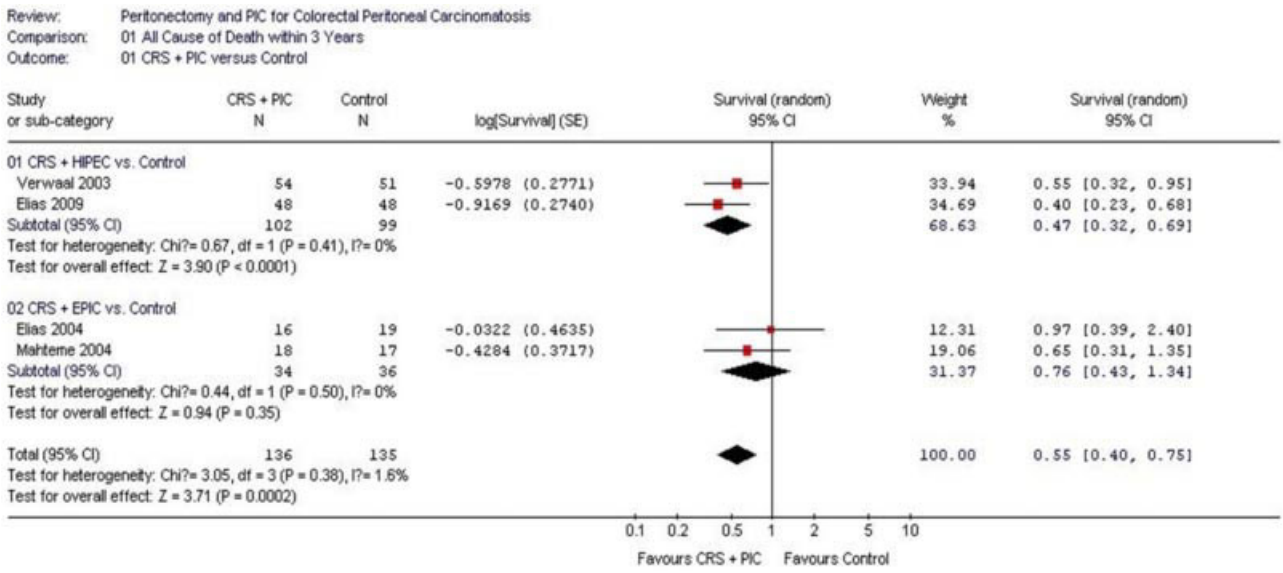

Fig. 2. Adopted from Ref. [48] with permission from Dr. Chris Cao; Forest plot of the hazard ratio (HR) of the overall survival at 3 years with perioperative intraperitoneal chemotherapy (PIC) versus control for colorectal peritoneal carcinomatosis where studies were analysed according to the regimens of intraperitoneal chemotherapy used, that is, 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 [48].

the use of systemic chemotherapy and local tumour ablation have expanded the criteria for resection [52]. This transition has taken place over a period of 20 years despite no level one evidence to support the superiority of surgical resection of colorectal liver metastases over other treatments [53]. Several studies have since also demonstrated that the survival outcome following a microscopically complete resection of colorectal liver metastases is similar to that of CS and HIPEC for peritoneal metastases from colorectal cancer [54–56].

In conclusion, this review has attempted to highlight the potentially distinct entity of peritoneal metastases in metastatic colorectal cancer and has systematically reviewed the literature to report the results of treatment from radical CS with HIPEC and that of palliative surgery and/or systemic chemotherapy. The results suggest that judicious selection of patients for CS and HIPEC to achieve a complete cytoreduction is necessary and is superior over the current best systemic chemotherapy. There is a body of evidence to support the treatment of CS and HIPEC for peritoneal metastases from colorectal cancer. A randomised trial that replicates and confirm these early results will establish and cement the position of this treatment as first line therapy for patients with resectable disease.

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