Peritoneal Carcinomatosis from Colon Cancer: A Systematic Review of the Data for Cytoreduction and Intraperitoneal Chemotherapy

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Abstract

A systematic review of the literature on the management of peritoneal carcinomatosis (PC) from colon cancer with cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) was undertaken using OVID Medline. Forty-six relevant studies were reviewed. Mean weighted overall morbidity following CRS and IPC was 49% (range 22–76%) and mortality was 3.6% (range 0–19%). Median overall survival ranged from 15 to 63 months, and 5-year overall survival ranged from 7 to 100%. This represents an improvement over historical treatment with systemic chemotherapy alone, even in the era of modern chemotherapeutic agents. Quality of life following surgery is initially decreased but improves with time and approaches baseline. Available data appear to support the treatment of PC from colon cancer with CRS and IPC. There is a large amount of variability among studies and few high-quality studies exist. Further studies are needed to standardize techniques.

Keywords
- colorectal cancer
- carcinomatosis
- intraperitoneal chemotherapy
- outcomes

Colon cancer presents with synchronous peritoneal spread in 5 to 10% of patients, and up to 20 to 50% of patients with recurrent disease will develop metachronous peritoneal disease.[1–4] Peritoneal carcinomatosis (PC) from colon cancer has traditionally been viewed as distant metastatic disease, with only a 12-month median survival even with systemic chemotherapy.[5] Long-term survival or cure in such cases was essentially unheard of. With advances in systemic chemotherapy, median survivals of 15 to 24 months have been achieved.[6–8] Nevertheless, cure does not appear to be attainable with systemic treatments alone.

A paradigm shift occurred when peritoneal disease was viewed as regional disease rather than diffuse metastatic disease, analogous to colorectal liver metastases in which local treatment can lead to long-term survival and even cure.[9] Cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) have been used in the setting of other peritoneal malignancies for such purpose with promising results. These techniques have been implemented in the management of PC secondary to colon cancer.

This review aims to summarize the current evidence for CRS and IPC in the management of PC from colon cancer.

Methods

A systematic literature search was performed using OVID Medline. The following medical subject terms and keywords and their combinations were used: Peritoneal Neoplasms (MeSH) (subheadings therapy, surgery, secondary, drug therapy), AND Colorectal Neoplasms (Mesh) (subheadings drug therapy, surgery, therapy, pathology), AND keywords cytoreductive OR cytoreduction, AND hyperthermia OR hyperthermic OR IPC. The search was limited to English language studies.

A total of 217 articles were identified. The titles and abstracts from the initial search were identified and reviewed for relevance. Review articles, editorials, and case reports were excluded. Studies were also excluded if most patients in the study had a primary malignancy other than colorectal cancer, namely those of appendiceal origin, as those were

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outside the scope of this review. Four full-text articles were unavailable and were excluded. Articles prior to the year 2000 were excluded to ensure contemporary data. Articles focusing on liver metastases in addition to PC were included and analyzed separately.

Weighted means were calculated for morbidity, and mortality and were weighted sample size.

Definitions

Cytoreductive Surgery

CRS for peritoneal disease refers to the surgical extirpation of all visible intraperitoneal tumor deposits. To accomplish this, the involved peritoneum is stripped and visceral resections may be performed. The procedure has been previously described in detail by Sugarbaker.[10]

Intraperitoneal Chemotherapy

IPC refers to the administration of chemotherapy directly into the peritoneal cavity. This can be performed intra- and/or postoperatively through a variety of techniques described as follows:

1. *Hyperthermic Intraperitoneal Chemotherapy (HIPEC)*: This technique refers to the administration of a heated chemotherapeutic agent to the peritoneal cavity intraoperatively, generally following complete CRS.
2. *Early Postoperative Intraperitoneal Chemotherapy (EPIC)*: This technique refers to the administration of a chemotherapeutic agent to the peritoneal cavity in the immediate postoperative period via an intraperitoneal catheter. It can be used alone or in combination with HIPEC.
3. *Sequential Postoperative Intraperitoneal Chemotherapy (SPIC)*: This technique refers to the administration of a chemotherapeutic agent to the peritoneal cavity in repeated cycles as an adjuvant treatment.

Peritoneal Cancer Index

The Peritoneal Cancer Index (PCI) is the most accepted metric to quantify the extent of peritoneal disease. It is most accurately assessed at the time of surgery, as the sensitivity in detecting peritoneal disease by computed tomographic (CT) scan has been shown to be 41.1% and the specificity 89%.[11] PCI is calculated by evaluating the size of peritoneal lesions in each of 13 abdominopelvic regions.[12] Lesion size (LS) is scored in each of the 13 regions (►**Fig. 1**) and summed to yield a score from 0 to 39.[10]

Completeness of Cytoreduction

The completeness of cytoreduction (CC) score provides an assessment of the amount of disease remaining after CRS. CC0 indicates that no macroscopic disease remains at the end of an operation. CC1 indicates that tumor nodules less than 2.5 mm in greatest diameter remain at the end of an operation. CC2 indicates that tumor nodules between 2.5 mm and 2.5 cm in greatest diameter remain. CC3 indicates that tumor nodules greater than 2.5 cm in greatest diameter remain.

The CC score is more commonly used in PC than the R-status that is traditionally used for primary malignancies. In PC, it is generally believed that an R0 status cannot be achieved, and therefore CC0 is equivalent to R1 (no gross residual disease). R2a indicates that minimal tumor nodules less than 5 mm remain. R2b indicates that gross tumor nodules greater than 5 mm and up to 2 cm remain. R2c indicates that extensive disease over 2 cm remains.

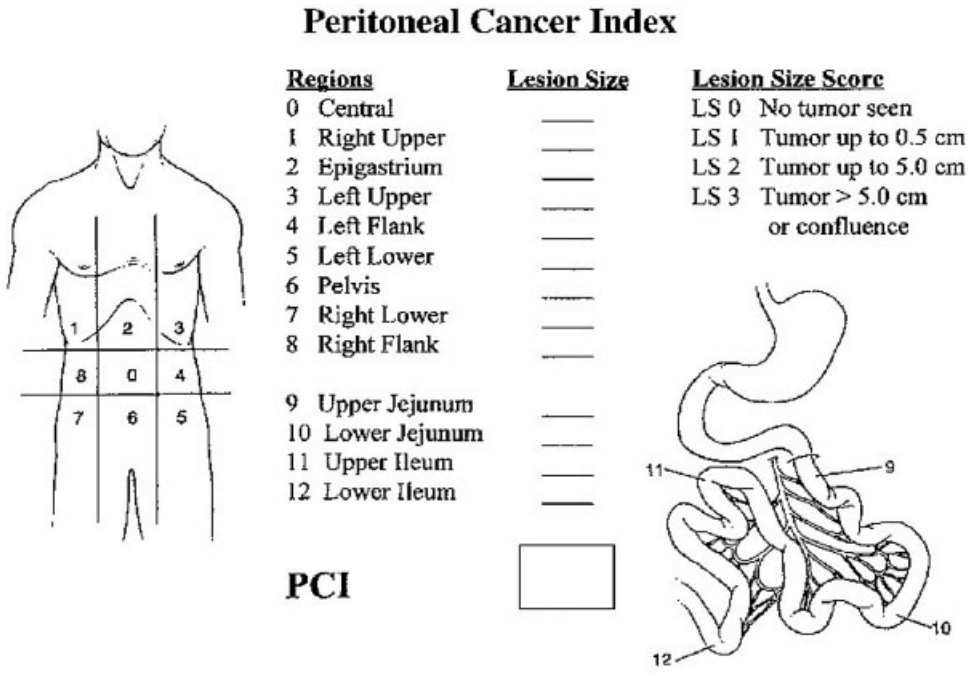

Fig. 1 Peritoneal Cancer Index (PCI) calculation for patients with peritoneal carcinomatosis.

The definition of complete cytoreduction varies among studies. It includes CC0 and R0 but may also include CC1, R1, and/or R2a.

Results

A total of 217 articles were identified. Following title and abstract review for exclusion criteria, a total of 46 articles were reviewed. Forty-three articles were included focusing on PC secondary to colon cancer, whereas three articles focused on patients with both PC and liver metastases secondary to colon cancer. The studies addressing liver metastases were reviewed separately below. Few level 1 or 2 studies (according to the Oxford Centre for Evidence-Based Medicine classification of levels of evidence)[13] have been undertaken and there is extensive variation among studies in terms of study design, patient selection, and operative and adjuvant treatments. Approximately 80% of the reviewed studies provide only level 4 evidence and consist of mainly retrospective case series. Patients range in terms of age, extent of disease, and anticipated treatment goals. Treatment options described included systemic chemotherapy, CRS, HIPEC, EPIC, SPIC, or combinations of these. The patient and treatment details from the reviewed studies are summarized in ►**Table 1**. The level of evidence of each study is also indicated. Overall outcomes and those specific to higher-quality studies are discussed in the following text.

Short-Term Outcomes

Overall morbidity following CRS and IPC ranged from 22 to 76% with a weighted mean of 49%. Major morbidity (including only studies reporting severe and grades 3–4 toxicity) ranged from 18 to 51% with a weighted mean of 24%. Perioperative mortality ranged from 0 to 19% with a weighted mean of 3.6%. The mortality and morbidity outcomes from the reviewed studies are summarized in ►**Table 2**.

To date, only one randomized clinical trial (RCT) on this topic has been completed and published. In 2003, Verwaal et al published an RCT comparing systemic chemotherapy with CRS and HIPEC plus systemic chemotherapy for PC from colorectal cancer.[5] This study randomized a total of 105 patients with colorectal or appendiceal adenocarcinoma to either standard treatment with systemic intravenous (IV) 5-fluorouracil (5-FU) and leucovorin (or irinotecan if prior 5-FU had been given) or to the investigational arm with CRS and HIPEC with intraperitoneal (IP) MMC for 90 minutes, followed by systemic chemotherapy as per the standard treatment. There were 51 patients assigned to the standard treatment arm, 44 of whom started treatment, and 54 patients assigned to the experimental arm, 49 of whom underwent surgery and 33 of whom started adjuvant chemotherapy. In terms of cytoreduction, 41% had a complete cytoreduction (R1/CC0). An 8% mortality rate was observed as a result of abdominal sepsis or pulmonary embolism. Grade 3 toxicity (according to the WHO scale) occurred in 66.7% of patients undergoing surgery, and grade 4 toxicity occurred in 45.8%, with leukopenia and small bowel fistula/leakage occurring most frequently.

Long-Term Outcomes

Mean weighted median overall survival for all studies reviewed was 27 months with a range of 15 to 63 months, and mean weighted 5-year overall survival was 27% with a range of 7 to 100%. Among studies reporting results after complete cytoreduction, mean weighted median survival was 31 months with a range of 12 to 48 months, and mean weighted 5-year overall survival was 31% with a range of 22 to 45%. The survival outcomes from the reviewed studies are summarized in ►**Table 3**.

In the RCT by Verwaal et al, median survival following systemic chemotherapy alone was 12.6 months, compared with 22.2 months following CRS, HIPEC, and adjuvant systemic chemotherapy ($p = 0.028$).[5] Progression-free survival was 12.6 months in the HIPEC arm compared with 7.7 months in the standard arm ($p = 0.02$). In patients who underwent complete cytoreduction, median survival was 45 months and 5-year survival was 45%. While this study provides level 1 evidence for CRS and HIPEC over systemic chemotherapy, several considerations must be noted in its application to patients with PC from colon cancer. The study included patients with colorectal primaries, but 17.1% of all patients included in the study had appendiceal primaries and 11.4% had rectal primaries, which may have different outcomes than colon cancer alone. Patients eligible for the study also represented a highly selected group of patients fit for major surgery. In addition, CC0 status was not achievable in most patients, a factor that was significantly associated with survival outcomes. These issues underscore the importance of patient selection for such procedures.

Overall, the study by Verwaal et al presents the highest-quality evidence currently available, but a major critique of the RCT was the use of 5-FU and leucovorin in the systemic chemotherapy arm, which was the standard of care at the time, rather than modern chemotherapy such as FOLFIRI/FOLFOX and bevacizumab. More recent retrospective studies have compared modern systemic chemotherapy with CRS and HIPEC. In a retrospective cohort study by Elias et al, 48 patients undergoing complete CRS (tumor deposits < 1 mm) and HIPEC (bidirectional chemotherapy with IV 5-FU and leucovorin and IP oxaliplatin) were matched to 48 patients who had systemic chemotherapy alone (control group).[7] An overall 5-year survival of 51% was observed in the HIPEC group compared with 13% in the control group ($p < 0.05$). The median survival was 62.7 months in the HIPEC group compared with 23.9 months in the control group ($p < 0.05$). Using a similar study design, Franko et al also found that patients receiving HIPEC had a significantly higher median survival than patients receiving only systemic chemotherapy (34.7 vs. 16.8 months, $p < 0.001$).[8] There remains no consensus on the chemotherapeutic regimen used, and indeed the role of IPC itself over CRS alone.

Outcomes by Intraperitoneal Chemotherapy Variables

A small number of studies with levels 2 to 4 evidence have investigated the variables associated with the administration and technique for IPC.

Table 1 Summary of studies of patients with peritoneal carcinomatosis secondary to colon cancer treated with CRS and/or IPC identified from systematic review

	Author	Year	*n*	Level of evidence	Groups	Type of IPC	Agent for IPC
1	Pestieau and Sugarbaker[33]	2000	104	4		HIPEC	MMC
2	Elias et al[34]	2001	64	4		HIPEC and EPIC	MMC ± cisplatin for HIPEC, MMC and 5-FU for EPIC
3	Pilati et al[35]	2003	34	4		HIPEC	MMC and cisplatin
4	Verwaal et al[5]	2003	105	1b	51 control	HIPEC vs. none	MMC
					54 experimental		
5	Elias et al[21]	2004	35	2b	16 EPIC group	EPIC vs. none	MMC and 5-FU
					19 non-EPIC group		
6	Glehen et al[36]	2004	53	4		HIPEC	MMC
7	Glehen et al[37]	2004	506	4		HIPEC (53.5%), EPIC (24.3%), or both (22.2%)	
8	Shen et al[38]	2004	77	4		HIPEC	MMC
9	Verwaal et al[39]	2004	102	4		HIPEC	MMC
10	Kecmanovic et al[40]	2005	18	4		HIPEC and EPIC	MMC for HIPEC, 5-FU for EPIC
11	Verwaal et al[41]	2005	117	4		HIPEC	MMC
12	Cavaliere et al[42]	2006	120	4		HIPEC	MMC and cisplatin or oxaliplatin and 5-FU and leucovorin
13	da Silva and Sugarbekar[43]	2006	70	4		HIPEC and/or EPIC	MMC for HIPEC, 5-FU ± MMC for EPIC
14	Füzün et al[44]	2006	29	4		HIPEC and EPIC	5FU for HIPEC, 5-FU for EPIC
15	Zanon et al[45]	2006	25	4		HIPEC	MMC
16	Bijelic et al[46]	2007	49	4		HIPEC and/or EPIC	MMC for HIPEC, 5-FU ± MMC EPIC
17	Elias et al[15]	2007	46	3b	23 HIPEC	HIPEC vs. EPIC	oxaliplatin and 5-FU and leucovorin for HIPEC, MMC and 5FU for EPIC
					23 EPIC		
18	Piso et al[47]	2007	32	4		HIPEC and EPIC	MMC and doxorubicin for HIPEC, 5-FU for EPIC
19	Franko et al[48]	2008	65	4		HIPEC	MMC
20	Verwaal et al[49]	2008	105	1b	51 control	HIPEC vs. none	MMC
					54 experimental		
21	Yan and Morris[50]	2008	50	4		HIPEC and EPIC	MMC for HIPEC, 5-FU for EPIC
22	Elias et al[7]	2009		3b	48 HIPEC	HIPEC vs. none	Oxaliplatin and 5-FU and leucovorin

(*Continued*)

Table 1 (*Continued*)

	Author	Year	*n*	Level of evidence	Groups	Type of IPC	Agent for IPC
					48 control		
23	Pelz et al[51]	2009	40	4		HIPEC	MMC
24	Swellengrebel et al[52]	2009	92	4		HIPEC	
25	Bretcha-Boix et al[53]	2010	20	4		HIPEC and EPIC	MMC or oxaliplatin and 5-FU for HIPEC, 5-FU for EPIC
26	Chua et al[54]	2010	56	4		HIPEC and EPIC (59%)	MMC
27	Elias et al[55]	2010	523	4		HIPEC (84%) or EPIC (16%)	MMC ± cisplatin or oxaliplatin ± irinotecan and 5-FU and leucovorin for HIPEC and MMC and 5-FU for EPIC
28	Franko et al[8]	2010		3b	67 HIPEC	HIPEC versus none	MMC
29	Saxena et al[56]	2010	63	4		HIPEC (19%), EPIC (27%), or both (54%)	MMC for HIPEC, 5-FU for EPIC
30	Vaira et al[57]	2010	40	4		HIPEC	MMC ± cisplatinum or oxaliplatin and 5-FU
31	Cavaliere et al[58]	2011	146	4		HIPEC	Cisplatin ± MMC or oxaliplatin and 5-FU and leucovorin
32	Chua et al[59]	2011	110	4		HIPEC (50%), EPIC (17%), or both (33%)	
33	Hill et al[22]	2011	62	4		HIPEC	MMC
34	Klaver et al[60]	2011	21	4		HIPEC (50%), EPIC (25%), or both (21%)	5-FU for EPIC
35	Quenet et al[19]	2011	146	2b	103 oxaliplatin/irinotecan	HIPEC	Oxaliplatin ± irinotecan and 5-FU and leucovorin
					43 oxaliplatin		
36	Stojadinovic et al[61]	2011	53	4		HIPEC	MMC
37	Cashin et al[14]	2012	151	4	69 HIPEC	HIPEC vs. SPIC (or none)	MMC ± 5-FU or oxaliplatin and irinotecan for HIPEC, 5-FU and leucovorin for SPIC
					57 SPIC		
38	Cashin et al[62]	2012	32	3b	16 HIPEC	HIPEC ± EPIC (56%) versus SPIC	oxaliplatin for HIPEC, 5-FU and leucovorin for EPIC
					16 SPIC		
39	Hompes et al[63]	2012	48	4		HIPEC	oxaliplatin and 5FU
40	Klaver et al[64]	2012	24	4		HIPEC (50%), EPIC (25%), or both (20.8%)	MMC or oxaliplatin for HIPEC, 5FU for EPIC
41	Passot et al[65]	2012	120	4		HIPEC	MMC ± irinotecan or oxaliplatin

Table 1 (*Continued*)

	Author	Year	*n*	Level of evidence	Groups	Type of IPC	Agent for IPC
42	Goéré et al[66]	2013	107	4		HIPEC (72%) or EPIC (28%)	oxaliplatin +/− irinotecan and 5-FU and leucovorin for HIPEC, MMC and 5-FU or cisplatin and doxorubicin for EPIC
43	Yonemura et al[67]	2013	142	4		HIPEC	MMC and cisplatin

Abbreviations: CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; 5-FU, 5-fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; MMC, Mitomycin C; SPIC, sequential postoperative intraperitoneal chemotherapy.

Type of Intraperitoneal Chemotherapy

A few studies have compared the different methods of IPC administration, including HIPEC, EPIC, and SPIC, or a combination of these. In a retrospective cohort study by Cashin et al, 151 patients were identified with peritoneal disease from colorectal cancer.[14] Of those patients, 69 underwent CRS and HIPEC (with IP MMC, oxaliplatin, or oxaliplatin and irinotecan) and 57 underwent CRS and SPIC (with IP 5-FU). Grades 3 to 4 90-day mortality occurred in 40.6% of HIPEC patients and 29.8% of SPIC patients ($p = 0.02$). The 90-day mortality was 4.3% in the HIPEC patients and 3.5% in the SPIC patients ($p = 0.98$). Patients in the HIPEC group improved overall survival with a median of 34 months and 5-year survival of 40%, compared with 25 months and 18%, respectively, in the SPIC group ($p = 0.01$). Among patients with CC0 resections only, the median survival was 39 months in HIPEC patients and 32 months in SPIC patients ($p = 0.3$). On multivariate analysis, the type of IPC was an independent prognostic factor, with improved outcomes in patients who received HIPEC compared with SPIC.

In a retrospective cohort study by Elias et al in 2007, 23 patients who underwent complete CRS and HIPEC with IP oxaliplatin and IV 5-FU/leucovorin for colorectal PC (HIPEC group) were compared with a matched group of 23 patients who underwent complete CRS with IP (normothermic) MMC and EPIC with IP 5-FU up to postoperative day 4 (EPIC group).[15] Mortality was 0% in the HIPEC group and 8.7% in the EPIC group, although this difference was not statistically significant. Overall morbidity was comparable, but on subgroup analysis a significant difference was noted in the rate of enteric fistulas (0% in the HIPEC group vs. 26% in the EPIC group, $p = 0.02$). Overall 5-year survival was 54% in the HIPEC group compared with 28% in the EPIC group. Although this difference was not statistically significant ($p = 0.22$), the power of the study may have been a contributing factor. Over a median follow-up period of 113 months, peritoneal recurrence occurred in 26% in the HIPEC group and 57% in the EPIC group ($p = 0.03$).

Although the role of hyperthermia was not specifically tested in these two studies, the improved outcomes with HIPEC over other types of IPC administered postoperatively without hyperthermia suggests that hyperthermia may play a role in improving the penetration of the IPC, as demonstrated in animal studies,[16–18] in the treatment of peritoneal disease.

Chemotherapeutic Agent for Intraperitoneal Chemotherapy

There was only one study identified that specifically investigated the chemotherapeutic agent(s) used for IPC for PC from colon cancer. Quenet et al conducted a bi-institutional prospective study on 146 patients who underwent CRS and HIPEC for colorectal PC.[19] Forty-three patients received IP oxaliplatin alone for HIPEC and 103 patients received IP oxaliplatin and irinotecan. All patients received intraoperative IV 5-FU and leucovorin following CRS. Although 90.4% of all patients received a CC0 resection, there was a significant difference between groups with 25.6% of patients in the oxaliplatin alone group compared with 2.9% of patients

Table 2 Mortality and morbidity of patients with peritoneal carcinomatosis secondary to colon cancer treated with CRS and/or IPC identified from systematic review

	Author	Subgroup	Mortality (%)	Morbidity (%)	Grades 1–2 morbidity	Grades 3–4 morbidity
1	Pestieau and Sugarbaker[33]					
2	Elias et al[34]		9.3	65.6		
3	Pilati et al[35]		0	35		
4	Verwaal et al[5]		8			
5	Elias et al[21]	EPIC	18.8			
6	Glehen et al[36]		4			23
7	Glehen et al[37]		4			22.9
8	Shen et al[38]		12	30		
9	Verwaal et al[39]					
10	Kecmanovic et al[40]		0	44.4		
11	Verwaal et al[41]		6			
12	Cavaliere et al[42]					22.5
13	da Silva and Sugarbekar[43]					
14	Füzün et al[44]		0	41		
15	Zanon et al[45]		4			24
16	Bijelic et al[46]					
17	Elias et al[15]	EPIC	8.7	56.5		
		HIPEC	0	47.8		
18	Piso et al[47]		0	34		
19	Franko et al[48]		1	60		
20	Verwaal et al[49]	HIPEC	7.4			
21	Yan and Morris[50]		0	76	46	18
22	Elias et al[7]					
23	Pelz et al[51]					
24	Swellengrebel et al[52]					
25	Bretcha-Boix et al[53]		2.5			40 (grades 2–4)
26	Chua et al[54]					
27	Elias et al[55]		3.3			31
28	Franko et al[8]					
29	Saxena et al[56]		0		52	31
30	Vaira et al[57]		2.5	55		
31	Cavaliere et al[58]		2.7			27.4
32	Chua et al[59]					
33	Hill et al[22]			48		
34	Klaver et al[60]					
35	Quenet et al[19]	All patients	4.1	47.2		
		Oxaliplatin	2.3	34.9		
		Oxaliplatin/irinotecan	4.9	52.4		
36	Stojadinovic et al[61]					
37	Cashin et al[14]	HIPEC	3			28
		SPIC	2			17
38	Cashin et al[62]	HIPEC	6			37

Table 2 (*Continued*)

	Author	Subgroup	Mortality (%)	Morbidity (%)	Grades 1–2 morbidity	Grades 3–4 morbidity
		SPIC	6			19
39	Hompes et al[63]		0	52.1		
40	Klaver et al[64]		0	62		
41	Passot et al[65]		3.8			21.8
42	Goéré et al[66]					
43	Yonemura et al[67]		0.7	42.9	25.4	17.6

Abbreviations: CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; SPIC, sequential postoperative intraperitoneal chemotherapy.

in the oxaliplatin/irinotecan group achieving CC1 or CC2 status ($p = 0.001$). An overall 30-day or in-hospital mortality of 4.1% was observed, with no difference between groups. However, the overall morbidity was 34.9% in the oxaliplatin alone group and 52.4% in the oxaliplatin/irinotecan group ($p = 0.05$). On multivariate analysis, the chemotherapeutic agent(s) used for HIPEC was associated with morbidity (OR = 2.35 for oxaliplatin/irinotecan vs. oxaliplatin alone). The 5-year and median overall survival rates were comparable between groups, at 41.8% and 40.8 months, respectively, for oxaliplatin alone, and 42.4% and 47 months, respectively, for oxaliplatin/irinotecan. The significantly increased morbidity, with no associated improvement in overall survival, suggests that irinotecan should not be added to oxaliplatin for IP administration.

Although there appears to be no benefit in adding irinotecan to oxaliplatin, several IPC regimens exist that have not been investigated or compared. Given the lack of studies specific to chemotherapeutic agents used for IPC for colon cancer, relevant data have to be extrapolated from studies with other primary malignancies. In a prospective cohort study, McConnell et al studied complications of patients with PC from a variety of primary sites (including 33% from colorectal cancer) following IPC with HIPEC and/or EPIC and different chemotherapeutic agents.[20] Eighty-five patients received HIPEC with IP MMC and EPIC with IP 5-FU (HIPEC and EPIC group) and 113 received HIPEC alone with IP oxaliplatin (HIPEC group). Significantly more grade III/IV complications (defined by the Clavien-Dindo grading system) occurred in the combined HIPEC and EPIC group compared with the HIPEC alone group (44.7 vs. 31% respectively, $p = 0.047$). While this study focused on the type of IPC (HIPEC and EPIC versus HIPEC alone), the two arms also differed in the chemotherapeutic agent used, and therefore it is difficult to conclude whether that group had a higher complication rate due to the type of IPC or the use of MMC rather than oxaliplatin. It also does not address survival outcomes among various chemotherapeutic agents. To date, no studies have specifically compared the use of MMC versus oxaliplatin.

Role of Intraperitoneal Chemotherapy

Because most studies have shown improved outcomes associated with a complete cytoreduction rather than from variations in IPC technique, the added value of IPC in addition to CRS has been questioned. Elias et al attempted to complete an RCT comparing patients who underwent complete CRS and then received either adjuvant systemic chemotherapy alone (control group) or EPIC and adjuvant systemic chemotherapy (EPIC group).[21] The EPIC regimen comprised IP MMC followed by IP 5-FU up to postoperative day 5. Unfortunately, only 35 patients were accrued, with 19 in the control group and 16 in the EPIC group. The recruited patients were analyzed and a 2-year overall survival of 60% was observed in both groups. However, there were three perioperative deaths in the EPIC group and none in the control group, although more patients in the EPIC group underwent simultaneous liver resections for liver metastases and had more extensive PC. Given the limited sample size and follow-up, it is difficult to make definitive conclusions on the specific role of IPC after complete CRS in the treatment of PC from colon cancer, and therefore larger and more rigorous studies are needed.

Quality of Life

Few studies have focused on quality of life following CRS and IPC. Only one study specifically addressed quality of life following surgery for PC of colonic origin. Hill et al prospectively identified 62 such patients undergoing CRS and HIPEC.[22] Emotional well-being, according to the Functional Assessment of Cancer Therapy Colon Scale (FACT-C), was significantly improved from baseline at 3 months postoperatively and remained above baseline at 6 and 12 months. The mean physical and functional well-being decreased to below baseline at 3 months but returned to near or above baseline at 6 and 12 months following surgery. A significant perceived decrease in role limitations due to physical health, as per the Short Form assessment (SF-36), occurred at 3 months, but this also returned to baseline by 6 and 12 months. Pain decreased from 3 months onward postoperatively. The incidence of depressive symptoms and depression tended to decrease over time from surgery, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D). Pain interference with functioning, as per the Brief Pain Inventory (BPI), increased above baseline at 3 months, but was decreased by 6 months and significantly below baseline by 12 months. Forty-seven percent of patients stated that they had returned to normal activity by 1 year following surgery. Sixty-one

Table 3 Survival outcomes of patients with peritoneal carcinomatosis secondary to colon cancer treated with CRS and/or IPC identified from systematic review

	Author	Subgroup	Median survival (mo)	Overall survival (%)					
				1 y	2 y	3 y	4 y	5 y	10 y
1	Pestieau and Sugarbaker[33]	Synchronous	NR					100	
		Metachronous	24					30	
2	Elias et al[34]				60.1	47.1	36	27.4	
3	Pilati et al[35]		18		31				
4	Verwaal et al[5]	HIPEC	22.4						
5	Elias et al[21]				60				
6	Glehen et al[36]	All patients	12.8	55	32			11	
		CC0	32.9	85	54			22	
7	Glehen et al[37]	All patients	19.2	72		39		19	
		CC0	32.4	87		47		31	
8	Shen et al[38]	All patients	16			25		17	
		R0/R1	28						
9	Verwaal et al[39]		19.9						
10	Kecmanovic et al[40]	All patients	15						
		CC0	19.9						
11	Verwaal et al[41]	All patients	21.8	75		28		19	
		R1	42.9	94		56		43	
12	Cavaliere et al[42]	All patients	19			25.8			
		CC0				33.5			
13	da Silva and Sugarbekar[43]		33	88		44		32	
14	Füzün et al[44]	All patients	21	72		13		7	
		CC0		87		37		25	
15	Zanon et al[45]		30.3	64	40				
16	Bijelic et al[46]	CC0/1	30					17	
17	Elias et al[15]	HIPEC						54	
		EPIC						28	
18	Piso et al[47]			96					
19	Franko et al[48]	All patients	15.3						
		R0/R1	20.2						
20	Verwaal et al[49]	HIPEC with R1	48					45	
21	Yan and Morris[50]		29	79	67	39			
22	Elias et al[7]	HIPEC	62.7		81			51	
23	Pelz et al[51]								
24	Swellengrebel et al[52]	All patients	25.6						
		R1	26.2						
25	Bretcha-Boix et al[53]							36	
26	Chua et al[54]		38	85	66	48			
27	Elias et al[55]		30.1	81		41		27	
28	Franko et al[8]	HIPEC	34.7						
29	Saxena et al[56]								
30	Vaira et al[57]		43						

Table 3 (*Continued*)

	Author	Subgroup	Median survival (mo)	Overall survival (%)					
				1 y	2 y	3 y	4 y	5 y	10 y
31	Cavaliere et al[58]	All patients	21		45				
		CC0	25		50				
32	Chua et al[59]	All patients	38	92		55		30	
		CC0	46						
33	Hill et al[22]	All patients	18	71.3	45.4				
		R0/R1	34	96.4	72.4				
34	Klaver et al[60]		28	71	43				
35	Quenet et al[19]	Oxaliplatin	40.8					41.8	
		Oxaliplatin/irinotecan	47					42.4	
36	Stojadinovic et al[61]	CC0/1	12						
37	Cashin et al[14]	HIPEC	34					40	
		CC0 with HIPEC	39						
		SPIC	25					18	
		CC0 with SPIC	32						
38	Cashin et al[62]	HIPEC	36.5						
		SPIC	23.9						
39	Hompes et al[63]			97.9	88.7				
40	Klaver et al[64]		35	83					
41	Passot et al[65]		36.2	77	51			33	
42	Goéré et al[66]							35	15
43	Yonemura et al[67]	All patients	24.4						
		CC0	25.9						

Abbreviations: CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; SPIC, sequential postoperative intraperitoneal chemotherapy.

percent of patients reported that their health was much or somewhat better by 12 months, whereas 17% reported that it was worse or much worse. Quality of life appeared to decrease initially but recovered by 6 to 12 months postoperatively.

Among studies looking at quality of life following CRS and HIPEC for all primary malignancies, similar outcomes have been shown. In a prospective study by Tsilimparis et al, health-related quality of life was studied in 90 patients undergoing CRS and HIPEC for a variety of primary malignancies, 21% of which were colorectal cancer.[23] Most quality-of-life outcomes decreased in the initial postoperative period and took approximately 24 months to return back or close to baseline. Symptoms were worse in the postoperative period, but pain, appetite, and constipation improved to near baseline by 1 month. Fatigue and diarrhea persisted for at least 6 months but improved by 24 to 36 months. Mean global health status, which represents a subjective perception of health, returned to baseline at 6 months and was greater than baseline at 24 months. Physical function recovered at 6 months and was greater than baseline at 36 months. Emotional function was at baseline by 12 months. Similarly, McQuellon et al found that quality of life and self-reported performance status decreased postoperatively following CRS and HIPEC in 64 patients, but showed improvement over the first year to at or above baseline.[24] Macri et al also found that physical and functional well-being were decreased at 3 months but were back at baseline by 6 months in 17 patients undergoing CRS and HIPEC.[25]

Treatment of Peritoneal Carcinomatosis with Synchronous Liver Metastases

A few studies have investigated the role of CRS and IPC in patients with colorectal cancer liver metastases in addition to PC. The studies are summarized in ►**Table 4**. Two level 4 studies have found that patients treated for PC with synchronous liver metastases had no worse survival than patients treated for PC without liver metastases with a median survival of 36 months and 2-year survival of 65%.[26,27] Morbidity of 31 to 39% and mortality of 0 to 2.3% were observed. However, there were differences between groups and not all patients underwent synchronous liver resections.

A level 3b cohort study by Maggiori et al matched patients with PC and liver metastases from colorectal cancer undergoing CRS, IPC (with HIPEC, EPIC, or both), and synchronous liver resection to those with only PC undergoing CRS and IPC.[28] Morbidity and mortality were similar between groups,

Table 4 Summary of studies of patients with peritoneal carcinomatosis and liver metastases secondary to colon cancer treated with CRS and/or IPC identified from systematic review

	Author	Year	*n*	Level of evidence	Subgroups	Type of IPC	Agents for IPC
1	Kianmanesh et al[26]	2007	43	4		HIPEC	MMC and cisplatin
2	Chua et al[27]	2009	55	4		HIPEC (12%), EPIC (22%), or both (67%)	MMC for HIPEC, 5-FU for EPIC
3	Maggiori et al[28]	2013	98	3b	37 liver metastases	HIPEC (43%), EPIC (49%), or both (8%)	oxaliplatin for HIPEC, MMC and 5-FU for EPIC
					61 no liver metastases	HIPEC (80%), EPIC (18%), or both (2%)	

Abbreviations: CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; 5-FU, 5-fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; MMC, mitomycin C.

but there was a trend toward increased perioperative mortality in the liver resection group (0 vs. 8% for the peritoneal disease only group vs. liver metastases group, respectively; $p = 0.051$). There was a significant decrease in overall survival in the PC plus liver metastases group compared with the PC alone group (median survival 32 vs. 49 months, 3-year survival 40 vs. 66%, and 5-year survival 26 vs. 43%, $p = 0.042$). Increased PCI was the main prognostic factor, followed by the synchronous resection of liver metastases. The worst survival was seen in patients with either a PCI of 12 or greater or the presence of three or more liver metastases. Though there was no difference in the number of peritoneal and distant metastases, the liver metastases group had significantly more recurrent liver metastases (61 vs. 12%, $p < 0.001$). CRS and IPC combined with liver resection may have a role in highly selected patients with a low burden of both peritoneal and liver disease.

Discussion

PC secondary to colorectal cancer has been traditionally viewed nihilistically. However, advances in the treatment of such patients have occurred with improved systemic chemotherapy and the application of CRS and IPC to PC of colorectal origin. Long-term survival has been demonstrated in patients with PC secondary to colon cancer undergoing CRS and IPC in multiple case series, cohort studies, and a randomized trial, with 5-year survival rates of up to 45% being achieved in patients undergoing complete cytoreduction and intraperitoneal chemotherapy.

Many aspects of CRS and IPC need to be further elucidated. A lack of standardization exists among treatment protocols and therefore a great degree of variability among studies on the topic. It is also important to recognize the generally low quality of studies in the literature on this topic. Further studies are needed to determine which patients benefit most from CRS and IPC and the optimal techniques for such procedures. Also, further data are needed specifically for patients with liver metastases in addition to PC.

In the past, several randomized trials have been attempted to answer some of these important questions, including the study by Elias et al in 2004[21] and an ACOSOG/USMCI trial by Stojadinovic.[29] Unfortunately, these studies were closed early due to poor accrual. Fortunately, several clinical trials are currently underway. A Swedish randomized study comparing systemic chemotherapy with CRS and EPIC with IP 5-FU and IV Isovorin in colorectal cancer has completed patient recruitment,[30] and a French multicenter randomized trial also comparing systemic chemotherapy with CRS and HIPEC with IP oxaliplatin and IV 5FU/LV has been initiated.[31] A randomized trial from Memorial Sloan Kettering comparing HIPEC with EPIC following CRS for colorectal and appendiceal primaries is also in process.[32] Though CRS and IPC have been gaining widespread interest, and even acceptance, this may also make it difficult to accrue patients for randomized trials, because both physicians and patients may be more reluctant to participate in studies where all patients are not offered CRS and/or IPC.

Low mortality and acceptable morbidity with an apparent improvement in long-term survival and possible cure following CRS and IPC for colon cancer have led to increasing acceptance among surgeons and patients of this treatment with an otherwise poor prognosis. Currently, support for CRS and IPC is increasing among both physicians and patients because PC from colon cancer in selected patients in whom a complete cytoreduction can be achieved. Ongoing studies will be necessary to standardize the procedure and optimize variables that currently exist among centers.

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