Review Article

Advances in therapeutics for peritoneal metastases from colorectal cancer: a narrative review

Mason A. Vierra[1], Ryan B. Morgan[2], Oliver S. Eng[3]

[1]University of Chicago Pritzker School of Medicine, Chicago, IL, USA; [2]Department of Surgery, University of Chicago Medical Center, Chicago, IL, USA; [3]Section of General Surgery and Surgical Oncology, Department of Surgery, University of Chicago Medicine, Chicago, IL, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: OS Eng; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Oliver S. Eng, MD. Assistant Professor of Surgery, Section of General Surgery and Surgical Oncology, Department of Surgery, University of Chicago, 5841 S. Maryland Ave., MC 5094, G205, Chicago, IL 60637, USA. Email: oeng@surgery.bsd.uchicago.edu.

Background and Objective: This review, as part of the special series titled "Peritoneal Carcinomatosis: History and Future," aims to describe the characteristics and disease burden of peritoneal metastasis from colorectal cancer (CRC), summarize its current treatments, and assess novel treatments that may aid in combatting this debilitating disease. The peritoneum is the 3rd most common site of metastasis from CRC. Patients with peritoneal metastases from CRC may be treated with a combination of cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic chemotherapy, but even with current care practices, the 5-year overall survival is around 40%. Various novel therapies are being tested in the hopes of improving outcomes for these patients.

Methods: A literature review was performed using MEDLINE/PubMed between June and October of 2021. Studies relating to the treatment of peritoneal metastases from CRC published between 1980 and 2021 were reviewed and data regarding the study design, patient population, and primary outcomes were assessed and recorded. Reviewed studies were categorized into 5 distinct categories: current treatments; additional modalities of intraperitoneal and systemic chemotherapy delivery; immunotherapy; monoclonal antibodies; and other.

Key Content and Findings: Today, peritoneal metastasis from colorectal cancer can be treated in a multimodality fashion which includes cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, and systemic chemotherapy. Regarding novel treatments, alternative modalities of chemotherapy delivery have shown some promise in non-randomized clinical settings, while other therapies are still primarily being tested in preclinical models; none have shown sufficient efficacy in large-scale trials to change the standard of care.

Conclusions: While there are several exciting therapies being tested in the treatment of peritoneal metastasis from CRC, it remains a debilitating disease that warrants continued efforts in the development of novel therapeutics.

Keywords: Peritoneal metastases; colorectal cancer (CRC); hyperthermic intraperitoneal chemotherapy (HIPEC)

Received: 16 November 2021; Accepted: 27 December 2021; Published: 30 March 2022.
doi: 10.21037/dmr-21-88
View this article at: https://dx.doi.org/10.21037/dmr-21-88

Introduction

Colorectal cancer (CRC) caused nearly 900,000 deaths and was newly diagnosed in 1.8 million patients worldwide in 2018, making it the 2nd leading cause of cancer deaths and the 3rd most diagnosed cancer (1,2). Carrying significant morbidity and mortality, it is estimated that anywhere from 55–75% of CRC patients will ultimately die from their cancer (3,4).

While patients with localized CRC can expect a 5-year

survival as high as 90% (5,6), it is estimated that 4–8% of CRC patients have peritoneal metastasis (PM) at the time of diagnosis and nearly 20% develop metachronous peritoneal disease, making the peritoneum the third most common site of CRC metastasis after the liver and lungs (7-11). Furthermore, PM from CRC is likely under-diagnosed and understudied, as peritoneal nodules are often too small to be detected on standard computed tomography (CT) or positive emission tomography (PET) (12,13), exploratory laparoscopy often leaves intra- and extra-peritoneal regions unexamined (14), symptoms may present late, and CRC patients with PM have historically been excluded from clinical trials due to their poor response to systemic chemotherapy relative to CRC patients without PM (15-17). Indeed, autopsy evidence suggests that the true incidence of PM from CRC is as high as 40% (18-20).

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-88/rc).

Methods

A systematic literature search was conducted using the MEDLINE/PubMed database. To identify relevant studies, the following search terms were used: "intraperitoneal chemotherapy", "colorectal cancer", "peritoneal carcinomatosis", "advanced colorectal cancer", "HIPEC", "EPIC", "novel therapies", and "adjuvant chemotherapy". Data regarding the study design, patient population, treatments received, safety and tolerability, and primary outcomes were assessed and recorded, and studies conducted or published prior to 1980 were excluded (*Table 1*). The quality of studies was independently evaluated by all researchers, with any disagreements regarding inclusion resolved through thorough assessment and discussion. The quality of relevant studies was noted in the manuscript.

Current treatments

The most common operative treatment for CRC with PM is cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC). While this treatment was first developed in the 1980's and 1990's, it gained wide use following several studies demonstrating an overall survival (OS) and progression-free survival (PFS) benefit compared to other modalities of treatment (21-29). One of the most notable of these studies was conducted in 2003, in which Verwaal *et al.* randomly assigned 105 patients with PM from CRC to either a "standard therapy" arm, consisting of systemic chemotherapy with or without palliative surgery, or an "experimental therapy" arm, consisting of CRS/HIPEC (22). After a median follow-up of 21.6 months, the median survival was 22.4 months in the experimental arm and 12.6 months in the standard arm. The authors also noted that the 2-year survival was more than twice as high in the CRS/HIPEC group, further demonstrating a significant survival benefit to CRS/HIPEC.

More recently however, the PRODIGE trial called into question the benefit of adding HIPEC to CRS (30). In this randomized, open-label, phase 3 trial conducted in France (NCT00769405), patients with PM from CRC either underwent CRS with oxaliplatin-based HIPEC or CRS alone, and all received perioperative systemic chemotherapy. After a median follow-up of 63.8 months no significant difference in OS or PFS was noted between the two groups, with the CRS/HIPEC group demonstrating median OS and PFS of 41.7 and 13.1 months, and the CRS-alone group demonstrating median OS and PFS of 41.2 and 11.1 months. However, there are several important findings to highlight from these results. Patients in both the CRS alone and the CRS/HIPEC group achieved a durable survival benefit from their treatment, with both groups experiencing a median overall survival exceeding 3 years. Further, the negative results from this trial may be attributable in part to the selected HIPEC regimen, as oxaliplatin was the only agent used in the trial and it was delivered at a lower dose and over a shorter perfusion time of 30 minutes compared to standard protocols used in the United States. Finally, a subsequent subgroup analysis demonstrated that HIPEC with oxaliplatin perhaps did improve OS and PFS in patients with an intermediate peritoneal cancer index (PCI) score between 11 and 15, and it is thus possible that HIPEC may provide a benefit in select patients.

Systemic chemotherapy in itself is also a standard treatment for PM from CRC, although systemic therapy alone has been historically associated with limited survival benefit. Various studies from the 1990s and early 2000s found that patients with PM of CRC origin treated with 5-fluorouracil and leucovorin had a median survival of 5.2 to 7.7 months (7,31-33). The addition of irinotecan and platinum-based analogs such as oxaliplatin to chemotherapeutic regimens has significantly improved this prognosis, with more recent studies demonstrating median survivals ranging from 6 to 24 months (28,34-38). However, a 2017 systematic review found little evidence in seven studies to support the use of neoadjuvant systemic

Table 1 The search strategy summary

Items	Specification
Date of search	07/01/2021–10/01/2021
Databases and other sources searched	MEDLINE/PubMed
Search terms used	Intraperitoneal chemotherapy, colorectal cancer, peritoneal carcinomatosis, advanced colorectal cancer, HIPEC, EPIC, novel therapies, adjuvant chemotherapy
Timeframe	01/01/1980–07/01/2021
Inclusion and exclusion criteria	Inclusion criteria: English language, published or available between 01/01/1980 and 07/01/2021, included patients with PM from CRC or evaluated novel therapies for PM from CRC Exclusion criteria: non-English language, abstracts, other malignancy unrelated to PM or CRC
Selection process	All three researchers independently assessed the quality of studies obtained from the literature review and consensus was required for inclusion in the manuscript

HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early post-operative intraperitoneal chemotherapy; PM, peritoneal metastasis; CRC, colorectal cancer.

chemotherapy in treating PM from CRC, although its analysis of 14 studies using adjuvant chemotherapy did demonstrate limited evidence of improved survival (39). Klaver et al. in 2013 found a significant OS and PFS benefit from the addition of 5-fluorouracil-based chemotherapy with oxaliplatin alongside targeted therapy of CRS or CRS/HIPEC, with the benefits even more pronounced when biological therapies, such as bevacizumab, panitumumab, or cetuximab, were incorporated as a first line treatment (40). Yet, few studies have directly compared biological agents and different timelines of administration against each other, making broad conclusions about the efficacy of systemic chemotherapy in treating PM from CRC difficult.

Today, most referral centers use a multidisciplinary approach of CRS/HIPEC alongside systemic chemotherapy, both adjuvant and neoadjuvant (41), in the treatment of PM from CRC. Regardless, even with optimal treatment, nearly half of patients experience disease progression or local recurrence in the 1st year after surgery, the 5-year overall survival is estimated at around 40%, and treatment itself may be associated with significant morbidity and mortality (24,25,42-50). Thus, it is imperative that novel therapies be investigated to better treat this debilitating and deadly disease.

Additional modalities of intraperitoneal and systemic chemotherapy delivery

One of the primary areas of investigation in the treatment of PM from CRC involves modifying and improving upon existing surgical techniques and administration of intraperitoneal or systemic chemotherapy, as summarized in *Table 2*.

Pressurized intraperitoneal aerosolized chemotherapy (PIPAC)

PIPAC laparoscopically delivers chemotherapy, most commonly oxaliplatin, as a pressurized aerosol, which theoretically should produce better tissue penetration and distribution of the cytotoxic agent compared to the traditional delivery system used in HIPEC (51,52). While early evidence suggests that it is safe with low toxicity and can stimulate disease regression in select patients with PM from CRC (53-56), a recent single-arm, phase II trial in patients with unresectable colorectal peritoneal metastases did report a high number of major and minor adverse events (57). Five clinical trials (NCT03868228, NCT03246321, NCT03280511, NCT03210298, and

Table 2 Modified intraperitoneal & systemic chemotherapy

Author, year, country/region	Participants (treatment *vs.* control)	Study design (treatment *vs.* control)	Outcome (treatment *vs.* control)
PIPAC			
Demtröder *et al.*, 2016, Germany	17	Retrospective analysis: response, safety, & survival after PIPAC	23% level III adverse events; 71% tumor response; 15.7 mo mean OS
Ellebæk *et al.*, 2020, Denmark	24	Prospective PIPAC-OPC1/2 data: response, safety, & survival after PIPAC	67% tumor response; 20.5 mo median OS; 8% severe adverse events
Kim *et al.*, 2021, Singapore	16	3+3 dose-escalation phase 1 study: safety & tolerability	19% pancreatitis; highest dose tolerated well
Rovers *et al.*, 2021, Netherlands	20	Phase II trial: safety, outcomes, OS & PFS after PIPAC	100% minor adverse events; 15% major adverse events; 8 mo median OS; 3.5 mo median PFS
EPIC			
Soucisse *et al.*, 2019, Australia	13 retrospective studies	Review of EPIC post-CRS/HIPEC for appendiceal & CRC with PM	Unclear: EPIC + CRS/HIPEC has potential OS benefit w/moderate complications
Park *et al.*, 2016, Korea	30 *vs.* 15	1:2 matched case-control study: EPIC *vs.* no EPIC	3-yr OS: 74.3% *vs.* 34.7%; 3-yr PFS: 53.0% *vs.* 7.5%
Elias *et al.*, 2007, France	23 *vs.* 23	Retrospective comparative study: EPIC *vs.* intraperitoneal chemohyperthermia (IPCH)	5-yr OS: 28% *vs.* 54%; PM recurrence: 57% *vs.* 26%; mortality: 8.7% *vs.* 0%; fistulas: 26% *vs.* 0%
Elias *et al.*, 2010, Europe & Canada	84 *vs.* 443	Retrospective cohort multicenter study: efficacy of CRS + intraperitoneal chemotherapy	Median OS: 32 *vs.* 31 mo; 5-yr OS: 30% *vs.* 25.5%
Lam *et al.*, 2015, Canada	37 *vs.* 56	HIPEC + EPIC *vs.* HIPEC alone	3-yr OS: 50% *vs.* 46%; 3-yr PFS: 21% *vs.* 6%; Grade III/IV complications: 43.2% *vs.* 19.6%
Glehen *et al.*, 2004, France	123 *vs.* 271	Retrospective multicenter study: safety, efficacy & prognosis of CRS/EPIC or CRS/IPCH	OS: 19.2 *vs.* 19.2; relative risk of major complications of EPIC: 1.4
Tan *et al.*, 2016, Singapore	42 *vs.* 69	Single center retrospective review: CRS/HIPEC/EPIC *vs.* CRS/HIPEC	Grade III+ complications: 58% *vs.* 25%; LOH stay: 16 *vs.* 13 days; OS & PFS comparable
Chua *et al.*, 2013, Australia	45 *vs.* 23 *vs.* 30	EPIC/HIPEC *vs.* EPIC alone *vs.* HIPEC alone	5-yr OS: 86% *vs.* 64% *vs.* 64%; PFS: 33 *vs.* 20 *vs.* 19 mo
Huang *et al.*, 2017, Australia	176 *vs.* 74	Retrospective study: EPIC + CRS/HIPEC *vs.* CRS/HIPEC alone in PM from appendiceal neoplasms	5-yr OS: 93% *vs.* 64.5%
McConnell *et al.*, 2013, Canada	85 *vs.* 113	HIPEC/EPIC *vs.* HIPEC alone	Grade III/IV complications: 44.7% *vs.* 31.0%; HIPEC/EPIC associated w/increased rate of complications
Memorial Sloan Kettering; 2023 completion	282	Ongoing phase II trial: EPIC *vs.* HIPEC	–
SPIC			
Armstrong *et al.*, 2006, Baltimore	205 *vs.* 210	Randomized Phase III trial: IV chemo + IP chemo *vs.* IV chemo alone post-op in ovarian cancer	OS: 65.6 *vs.* 49.7 mo; PFS: 23.8 *vs.* 18.3 mo

Table 2 (*continued*)

Table 2 (*continued*)

Author, year, country/region	Participants (treatment *vs.* control)	Study design (treatment *vs.* control)	Outcome (treatment *vs.* control)
Cashin *et al.*, 2016, Sweden	24 *vs.* 24	CRS/SPIC *vs.* systemic chemotherapy	Premature termination; 2-yr OS: 54% *vs.* 38%; median OS: 25 *vs.* 18 mo; PFS: 12 *vs.* 11 mo
Mahteme *et al.*, 2004, Sweden	17 *vs.* 18	CRS/SPIC *vs.* systemic chemotherapy	5-yr OS: 28% *vs.* 5%; median OS: 32 *vs.* 14 mo
Cashin *et al.*, 2012, Sweden	16 *vs.* 16	Matched case-control study: CRS/SPIC *vs.* CRS/HIPEC	OS: 23.9 *vs.* 36.5 mo; PFS: 13 *vs.* 22.8 mo
Cashin *et al.*, 2012, Sweden	57 *vs.* 69	Cohort study: CRS/SPIC *vs.* CRS/HIPEC	5-yr OS: 18% *vs.* 40%; OS: 25 *vs.* 34 mo
"Bidirectional chemotherapy"			
Sgarbura *et al.*, 2016, France	6	Pilot study: pre-op intraperitoneal chemo in unresectable cases	33% completed the protocol; 50% grade 3 toxicities; 0% major disease improvements
Yonemura, 2012, Japan	86	Neoadjuvant IP chemotherapy (NIPS) in gastric cancer: efficacy & survival	(+) cytology: 70.8% before *vs.* 22.9% after NIPS
2nd-look & adjuvant HIPEC			
Elias *et al.*, 2008, France	29	Prospective study: 1-yr post-CRS/HIPEC 2nd-look surgery in detecting PM in patients w/o signs of recurrence	PM detected and treated in 55% of patients
Elias *et al.*, 2011, France	41	2nd-look surgery + HIPEC 1-yr post-op in asymptomatic patients at high risk of developing PM	PM detected and treated w/HIPEC in 56% of patients; 5-yr OS: 90%; 5-yr PFS: 44%; 17% recurrence 9.7% grade III/IV complications
Baratti *et al.*, 2017, Italy	22	1:2 matched case control: adjuvant CRS/HIPEC in patients w/o systemic disease at a high risk of metachronous PM	5-yr OS: 81.3% *vs.* 70.0%; 5-yr PM incidence: 9.3% *vs.* 42.5%; Grade III/IV adverse events: 18.2% *vs.* 25.0%
Sloothaak *et al.*, 2014	7 comparative & 5 cohort studies	Systematic review: adjuvant HIPEC to prevent development of PM	HIPEC associated w/reduced incidence of PM & improved OS
Klaver, 2019, Netherlands (COLOPEC)	100 *vs.* 102	HIPEC + systemic chemo *vs.* Systemic chemo alone in patients at high risk of PM development	PM development: 19% *vs.* 23%; 18-mo PFS: 80.9% *vs.* 76.2%
Goéré *et al.*, 2020, France (PROPHYLOCHIP)	75 *vs.* 71	2nd-look CRS/HIPEC *vs.* Surveillance in patients at high risk of PM development	3-yr PFS: 44% *vs.* 53%; Grade III/IV complications in 41% of treatment group
Sánchez, *et al.*, ongoing, Spain (HIPECT4)	100 *vs.* 100	Ongoing RCT: adjuvant HIPEC in preventing PM in high-risk patients	Ongoing
Perioperative Chemo + CRS/HIPEC			
Netherlands (CAIRO6)	40 *vs.* 40	Phase II RCT: perioperative systemic chemo + CRS/HIPEC *vs.* CRS/HIPEC alone	Macroscopic complete CRS/HIPEC: 89% *vs.* 86%; post-op morbidity: 22% *vs.* 33%

PIPAC, pressurized intraperitoneal aerosolized chemotherapy; EPIC, early post-operative intraperitoneal chemotherapy; SPIC, sequential postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; OS, overall survival; PFS, progression-free survival; CRC, colorectal cancer; PM, peritoneal metastasis; RCT, randomized control trial; mo, months.

NCT02604784) are currently investigating the safety and efficacy of this novel procedure in PM from CRC (49).

Early post-operative intraperitoneal chemotherapy (EPIC)

EPIC administers chemotherapy, typically mitomycin C or 5-fluorouracil, for 5 days following surgery. Introduced in the 1990s in an attempt to reduce peritoneal recurrence following cytoreduction (58,59), current research on its use in patients with PM from CRC is entirely retrospective in nature and its benefits are inconclusive (60). For example, a 1:2 matched case-control study found that the administration of EPIC in patients undergoing CRS for PM from CRC improved OS and PFS compared to controls who did not receive EPIC (61). Conversely, when EPIC has been compared head to head with HIPEC, it has not shown superiority in regard to OS or PFS and has been associated with worse side effects across patients with various primary tumors, including colorectal (23,24,62-64). While current evidence does not support the addition of EPIC to CRS/HIPEC, Chua et al. showed that the combination of the two improved OS and PFS in patients with colorectal peritoneal carcinomatosis compared to either treatment alone (65), and the combination has also produced favorable results in patients with peritoneal dissemination from primary tumors of appendiceal origin (66). However, this combination has been associated with an increased risk of postoperative complications, with one study finding that EPIC + HIPEC produced higher rates of grade III/IV complications compared to HIPEC alone (44.7% *vs.* 31.0%), and that on multivariate logistic regression it was associated with increased complications in patients with peritoneal malignancies (67). The ongoing ICARuS trial (NCT01815359) is the first randomized control trial to prospectively compare EPIC, which will use floxuridine and leucovorin, and HIPEC with mitomycin C, for treatment of peritoneal metastasis of appendiceal and colorectal origin.

Sequential postoperative intraperitoneal chemotherapy (SPIC)

SPIC is a form of sequential EPIC administered for 6 months post-CRS. While it has demonstrated a survival benefit in treating PM from ovarian cancer (68), it has only been sparsely investigated in PM from CRC origin, with just a handful of trials and case-control studies in the literature. A randomized trial that was terminated prematurely along with a non-randomized comparative study found that CRS/SPIC did confer a survival benefit compared to systemic chemotherapy alone (69,70), but the role of SPIC cannot be extrapolated from these studies as there were no control groups undergoing CRS without SPIC. SPIC has been compared to HIPEC alone in both a case-control and a cohort study, both of which demonstrated superior OS and PFS in the HIPEC group (71,72). Nonetheless, its use should be evaluated in conjunction with the standards of care to determine whether it has any use as an adjuvant therapy to CRS/HIPEC.

"Bidirectional" chemotherapy

A "bidirectional" chemotherapy approach involves the simultaneous use of intraperitoneal chemotherapy and systemic chemotherapy preoperatively in patients with advanced, unresectable tumors with the goal of making complete surgical resection possible. One pilot study evaluated a bidirectional regimen of oxaliplatin-based intraperitoneal chemotherapy and FOLFIRI-based systemic chemotherapy in six patients with unresectable PM from CRC (73). The study reported several side effects and complications, but overall the regimen was tolerated well and the researchers recommended a phase I or II trial to determine the optimal oxaliplatin dose and the regimen's efficacy. This approach has also been investigated in gastric cancer, with promising results (74).

2nd-look and prophylactic/adjuvant HIPEC

Second-look laparotomy and prophylactic HIPEC has been investigated in patients at a high risk for recurrence or metastasis. Elias et al. found that in patients who were asymptomatic and had no signs of recurrence or metastasis on imaging studies 13 months after resection of an aggressive primary tumor, a second-look operation was able to detect and diagnose peritoneal metastasis in approximately 55% of cases (75,76). Several other studies have found a benefit to prophylactic HIPEC in local tumors at a high-risk for peritoneal dissemination (77,78).

However, two clinical trials, the COLOPEC (NCT02231086) trial and more recently the PROPHYLOCHIP (NCT01226394), failed to find a difference in OS or PFS in this high-risk patient population (79,80). The COLOPEC trial aimed to determine whether adjuvant HIPEC could prevent the development of PM in patients with colon cancer at a high risk for peritoneal spread (80). Conducted in

9 Dutch centers, 204 patients were randomly assigned to receive either adjuvant systemic chemotherapy alone or adjuvant HIPEC followed by standard adjuvant systemic chemotherapy. Progression to PM did not significantly differ between the two groups, with 19% of patients in the experimental arm developing PM compared to 23% in the control arm. During diagnostic laparoscopy at 18 months there was no statistically significant difference in peritoneal-free survival (80.9% for the experimental group *vs.* 76.2% in the control group.) PROPHYLOCHIP (NCT01226394) was conducted in 23 hospitals in France and randomized 150 patients with CRC at a high risk for developing PM and who had already received 6 months of standard systemic adjuvant chemotherapy to either surveillance or second-look surgery plus HIPEC (79). After a median follow-up of 50.8 months the 3-year disease-free survival was 53% in the surveillance group and 44% in the second-look surgery group, demonstrating no benefit to exploratory laparotomy and HIPEC over surveillance alone. Additionally, 41% of patients in the second-look surgery group had grade 3–4 complications, the most common of which were abdominal hemorrhage or digestive leakage.

Various clinical trials, including the ongoing HIPECT4 (NCT02614534) trial, which uses mitomycin C as adjuvant HIPEC as opposed to the oxaliplatin used in the PROPHYLOCHIP and COLOPEC trials, will further investigate the utilization of HIPEC in preventing PM from CRC in high-risk patients (49).

Perioperative chemotherapy with CRS/HIPEC

While the role of adjuvant and neoadjuvant systemic chemotherapy in treating PM from CRC has already been discussed, another area of investigation is the use of perioperative systemic chemotherapy in conjunction with CRS/HIPEC.

The CAIRO6 (NC02758951) study, an open-label, phase 2 randomized clinical trial performed in Dutch tertiary referral centers, was the first to prospectively compare perioperative systemic chemotherapy in conjunction with CRS/HIPEC versus CRS/HIPEC alone in patients with resectable colorectal peritoneal metastases (76,81). With 40 patients randomized to each arm, the trial found no significant differences in proportion of macroscopic complete CRS/HIPEC between the two groups (89% in the experimental group *vs.* 86% in the control group). Similarly, post-operative morbidity did not differ significantly between the two groups (22% in the experimental group *vs.* 33% in the control group). Most of the intraoperative and postoperative characteristics did not significantly differ between the two groups as well, although the experimental group did show a lower median PCI score (5 *vs.* 12), a lower rate of ostomy formation (19% *vs.* 43%) and reduced median length of hospital stay (8 *vs.* 11 days). Despite these negative results, the authors noted that the addition of perioperative systemic chemotherapy was considered safe and capable of inducing a response in patients, and felt that their results justified a phase 3 trial.

Immunotherapy

Intraperitoneal immunotherapy is a novel approach in the treatment of PM from CRC, and while most studies in the field are still nascent and inconclusive and have been primarily performed in animal models, they nonetheless represent exciting first steps. These studies are summarized in *Table 3*.

CAR-T cell therapy

CAR-T immunotherapy involves collecting and modifying T-cells to target cancer-specific antigens (82) and is currently being investigated in both localized and disseminated solid tumors (83). Upregulated in CRC (84), CEA has arisen as a potential target for this type of immunotherapy (85). Early studies in patients with metastatic CRC not limited to the peritoneum demonstrated the feasibility of this approach, though sample sizes were small and significant side effects were noted in certain patients (86,87). In 2016, Katz *et al.* investigated intraperitoneal administration of CAR-T cells in a murine model of PM from CRC. The researchers found that the treatment induced significant cancer cell lysis and provided prolonged protection against CEA positive peritoneal tumors, especially when administered in conjunction with antibodies that suppressed myeloid-derived suppressor cells and regulatory T cells that had proliferated in the peritoneal tumors (88). Another potential target of CAR-T therapy in PM from CRC is the surface antigen folate receptor-α (FRα) (89). In a murine model of ovarian, colorectal and breast cancer, however, Song *et al.* found that while a combination of CAR-T cells with a co-stimulatory molecule designed to target FRα did improve T-cell persistence, it did not produce adequate anti-tumor activity and did not demonstrate consistent

Table 3 Immunotherapy

Author, year, country/region	Participants	Study design	Outcome
CAR-T cell therapy			
Katz *et al.*, 2015, Boston	6	Phase I trial: CAR-T cell therapy in patients w/CEA (+) liver metastases from CRC	0% grade III/IV adverse reaction; CEA levels decreased 37% w/IL2 support
Parkhurst *et al.*, 2011, Maryland	3	CAR-T cell therapy in patients w/CEA (+) metastatic CRC	74–99% decrease in CEA levels in all patients; severe transient inflammatory colitis in all patients
Katz *et al.*, 2016, Boston	Murine model of PM from CRC	Intraperitoneal CAR-T cell therapy targeting CEA	Treatment induced cancer cell lysis & protection from CEA + tumors
Song *et al.*, 2011, Philadelphia	Murine model of PM from CRC	Intraperitoneal CAR-T cell therapy targeting FRα	Treatment did not produce anti-tumor activity
Cancer vaccines			
Alkayyal *et al.*, 2017, Canada	Murine model of PM from CRC	Intraperitoneal cancer vaccine of tumor cells infected with Maraba virus	Treatment induced cytotoxic immune cell migration, reduced tumor burden & improved OS
Liang *et al.*, 2016, China	Murine model of CRC	Intraperitoneal recombinant plasmid targeting FRα	Treatment induced NK cell and $CD8^+$ T cell response & reduced tumor burden
Oncolytic vaccinia virus			
Heo *et al.*, 2013, South Korea	30	Phase II dose-finding trial: determine optimal JX-594 dose in hepatocellular carcinoma	JX-594 showed oncolytic & immunotherapy moa; tumor response & survival were dose-related
Breitbach *et al.*, 2015, Canada	10+ studies	Review summarizing all available data on JX-594 oncolytic vaccinia virus	JX-594 tolerable & safe; anti-tumor activity in hepatocellular carcinoma
Lee *et al.*, 2020, Korea	Murine model of PM from CRC	Oncolytic vaccinia virus with granulocyte-macrophage colony-stimulating factor	Treatment activated immune cells, potentiated immune checkpoint inhibitor activity, & suppressed PM progression

CAR, chimeric antigen receptor; PM, peritoneal metastasis; CRC, colorectal cancer; CEA, carcinoembryonic antigen; OS, overall survival; NK, natural killer.

localization (90).

Cancer vaccines

Cancer vaccines represent another potential immunotherapy, sensitizing the immune system to cancer cells. In a murine model of PM from CRC, Alkayyal *et al.* found that intraperitoneal injection of tumor cells infected with an oncolytic Rhabdovirus, Maraba virus, induced the recruitment of cytotoxic natural killer cells to the peritoneal cavity and was associated with reduced tumor burden and improved OS, even in mice with bulky peritoneal carcinomatosis (91). Similarly, Liang *et al.* evaluated the intraperitoneal administration of a recombinant plasmid that targeted FRα (the same antigen targeted by Song *et al.*) in a colon cancer murine model, and found that the treatment induced a significant response by natural killer cells and $CD8^+$ T cells and led to substantial tumor reduction (92).

Oncolytic vaccinia virus

Immune checkpoint inhibitors when used alone have shown limited efficacy in treating CRC (93-95), and some researchers have therefore turned to oncolytic virotherapy, a novel type of immunotherapy that essentially acts as an in-situ cancer vaccine, to treat this deadly malignancy. The oncolytic vaccinia virus mJX-594 (JX) is armed with granulocyte-macrophage colony-stimulating factor (GM-CSF), which is upregulated in various cancers and has been shown to stimulate immune cell maturation and activity (96,97). Having demonstrated oncolytic and immunostimulatory activity in preclinical models and clinical models of liver cancer (98,99), Lee *et al.* tested JX in a murine model of PC from MC38 colon cancer.

Table 4 Monoclonal antibodies

Author, year, country/region	Participants	Study design	Outcome
MOC31PE immunotoxin			
Wiiger *et al.*, 2014, Norway	Ovarian cancer cell lines B76 and HOC7	Investigate MOC31PE on protein synthesis, cell proliferation, and gene expression in ovarian cancer cell lines	MOC31PE reduced protein synthesis, suppressed cell viability & migration, and altered gene expression
Flatmark *et al.*, 2013, Norway	Peritoneal and mucinous tumor cells from animals and humans	MOC31PE +/– Mitomycin C on protein synthesis & cell proliferation in *ex-vivo* tumor cells	MOC31PE + Mitomycin inhibited cell growth & induced apoptosis; addition of MOC31PE to Mitomycin C based chemo had additive benefits on suppression of peritoneal tumor cells
Andersson *et al.*, 2009, Norway	Murine model of cervical cancer; *ex vivo* model of human breast, cervical, and prostate cancer	Cyclosporin A + various immunotoxins (including MOC31PE) in protein synthesis, cell viability, & apoptosis of tumor cells	Synergistic benefits of Cyclosporin A & MOC31PE in various cancer types
Frøysnes *et al.*, 2021, Norway (ImmunoPeCa)	21	Phase I trial: intraperitoneal MOC31PE immunotoxin 1 day post-CRS/HIPEC	Drug well-tolerated; 100% developed neutralizing antibodies; 3-year OS: 78%; 3-year PFS: 33%; median PFS: 21 mo
Catumaxomab			
Ströhlein *et al.*, 2009, Germany	5 Catumaxomab studies	Review of intraperitoneal immunotherapies that prevent PM from gastrointestinal malignancies	Catumaxomab demonstrates anti-tumor activity & improvement of malignant ascites symptoms
Jäger *et al.*, 2012, Germany	165 *vs.* 85	Phase II/III study: Catumaxomab *vs.* paracentesis in malignant ascites secondary to epithelial cancers	Catumaxomab eliminated EpCAM + tumor cells & activated peritoneal T cells
Thadi *et al.*, 2018, Philadelphia	7 Catumaxomab studies	Review of intraperitoneal immunotherapies for PM	Catumaxomab reduces ascites production, improves and prolongs functional quality of life, and may prolong OS in patients with malignant ascites from ovarian & gastric cancer origins
Bezan *et al.*, 2013, Austria	1	Case report: 78-year-old patient w/PM from CRC treated w/ Catumaxomab	Catumaxomab suppressed malignant ascites & may have had systemic anti-tumor effects

HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; OS, overall survival; PFS, progression-free survival; CRC, colorectal cancer; PM, peritoneal metastasis.

The researchers found that the oncolytic vaccinia virus suppressed peritoneal cancer progression and malignant ascites formation, activated peritoneal dendritic cells and $CD8^+$ T cells, selectively destroyed peritoneal colon cancer cells, and even potentiated the activity of immune checkpoint inhibitors and anti-cancer immune cells (100).

Monoclonal antibodies

While three biologic agents—Bevacizumab, Cetuximab, and Panitumumab—are currently approved as first-line treatments for metastatic CRC, several other monoclonal antibodies are under investigation as potential treatments for PM from CRC, as summarized in *Table 4*.

MOC31PE immunotoxin

MOC31PE immunotoxin is composed of two parts: a monoclonal antibody that targets epithelial cell adhesion molecule (EpCAM), an antigen commonly expressed in

CRCs, and pseudomonas exotoxin A. MOC31PE can enter cancer cells that express EpCAM, upon which its toxin causes cell death by inactivating vital cell processes. It demonstrated anti-cancer activity in preclinical testing (101-103) and was tested in patients with PM from CRC in the ImmunoPeCa trial (NCT02219893), a dose-escalating phase 1 trial conducted in 2017 (104). In this trial, 21 patients undergoing CRS/HIPEC for PM from CRC were administered the MOC31PE immunotoxin intraperitoneally the day after surgery at four different dose levels. The researchers found that the drug was safe and well-tolerated, with no dose-limiting toxicity observed. MOC31PE concentrations in the peritoneal fluid were considered to be in the cytotoxic range, though it was not absorbed systemically in any appreciable amount. All patients developed neutralizing antibodies. At 34 months follow-up, the estimated 3-year OS was 78% and the median PFS was 21 months, and the researchers concluded that these results warrant further investigation into the efficacy of MOC31PE immunotoxin at treating PM from CRC (105).

Catumaxomab

Catumaxomab is a rat-mouse hybrid monoclonal antibody that targets EpCAM. With demonstrable antineoplastic activity (106,107), in 2009 it was approved in Europe for treating malignant ascites caused by peritoneal carcinomatosis (108,109). While several studies have shown its efficacy in treating malignant ascites from primary ovarian and gastric cancers (110), its use in CRC and PM from CRC is still largely unexplored. However, a single case report of a 78-year-old patient with peritoneal carcinomatosis of colonic origin treated with catumaxomab found that it suppressed malignant ascites and may have even had systemic antitumor effects (111), and perhaps it warrants further investigation as an adjuvant treatment for PM from CRC.

Other

Radspherin

Radspherin is an alpha-emitting radioactive microparticle drug created by the privately held Norwegian pharmaceutical company Oncoinvent. Designed to distribute localized radiation to cancer cells, Oncoinvent hopes that it will be able to treat metastatic cancers in body cavities. The company claims that in pre-clinical models it has demonstrated anti-cancer activity, has increased overall survival, and has produced little to no toxicity. It is currently being investigated in two separate phase 1 open label clinical trials: RAD-18-001 (NCT03732768) for the treatment of peritoneal carcinomatosis from ovarian cancer and RAD-18-002 (NCT03732781) for the treatment of peritoneal carcinomatosis from colorectal carcinoma. In the RAD-18-002 trial, Radspherin will be administered as an intraperitoneal injection following CRS/HIPEC.

Conclusions

Peritoneal metastases from CRC remains a challenging disease process that, even when treated with a multidisciplinary approach including CRS/HIPEC and systemic chemotherapy, carries significant morbidity and mortality. Various novel therapies are currently being tested to aid in treating this disease, with some promising results, although preliminary. The continued development of these therapies and others will move the paradigm forward with the hope of impacting outcomes in years to come.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research* for the series “Peritoneal Carcinomatosis: History and Future”. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-88/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-88/coif). The series “Peritoneal Carcinomatosis: History and Future” was commissioned by the editorial office without any funding or sponsorship. OSE served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Digestive Medicine Research* from August 2020 to September 2022. OSE received grants from Appendix Cancer Pseudomyxoma Peritonei Foundation Research Grant with the payment made for his institution. OSE had a

participation on Verywell Health-Medical Advisory Board. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-21-88
Cite this article as: Vierra MA, Morgan RB, Eng OS. Advances in therapeutics for peritoneal metastases from colorectal cancer: a narrative review. Dig Med Res 2022;5:18.