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Colorectal cancer peritoneal metastases: biology, treatment and next steps

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Abstract

The presence of peritoneal metastases in patients with advanced colorectal cancer is associated with poor prognosis but the mechanisms for this are unclear. This review summarises the current knowledge of the pathophysiology, clinical features, prevalence, prognosis, and molecular biology of peritoneal metastases and the risk factors for the development of peritoneal metastases following resection of a primary colorectal tumour. Furthermore, the evidence for treatment strategies are described including cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, early post-operative intraperitoneal chemotherapy, sequential post-operative intraperitoneal chemotherapy and emerging novel strategies. Active areas of research should include the identification of individuals at high risk of peritoneal metastases after curative resection of primary tumour, development of a surveillance program for high-risk patients, optimisation of systematic therapies and investigation of the use of prophylactic intraperitoneal chemotherapy for selected high-risk patients.

Keywords

Colorectal cancer; peritoneal metastases; treatment; biology; intraperitoneal chemotherapy

1 Introduction

The peritoneum is the third commonest site of metastatic disease in colon cancer and the fourth commonest in rectal cancer [1], and is associated with inferior overall survival (OS) compared with other sites of metastatic disease [2-5]. This is reflected in the recent 8th edition of TNM staging where peritoneal metastases are now classified as pM1c [6]. The mechanisms underlying this poor prognosis are unclear. Here we will provide an overview of the pathophysiology, clinical symptoms, diagnosis, and risk factors for peritoneal metastases of colorectal cancer (pmCRC). Furthermore, we will discuss current treatment strategies for pmCRC, and areas of active research.

2 Prevalence

Peritoneal metastases are diagnosed in around 10% of all CRC patients [7, 8], and are present in around 30% of all metastatic colon cancer patients and 5% of all metastatic rectal cancer patients [1]. Diagnosis is either made whilst patients are in follow up after surgical resection of the primary tumour (metachronous metastases) [7, 8], or at the time of first presentation of CRC (synchronous metastases) [4, 7, 8]. The peritoneum is the only site of distant metastasis in 2%-5% of metastatic CRC (mCRC) patients [4, 7].

3 Risk factors for the development of peritoneal metastases

For patients undergoing curative resection of primary CRC, factors associated with increased risk of developing peritoneal metastases include young age [9], locally advanced primary tumour/lymph node involvement [8-13], particularly if there is synchronous metastatic spread to the peritoneum [14], liver [8], or ovary [14]. Other risk factors include an involved positive resection margin [10], or if the primary

resection was performed as an emergency procedure due to obstruction or perforation of the primary tumour [12-14]. High risk histological features that were reported include: mucinous histology [10, 12, 13], infiltrating growth pattern [13], perineural invasion [8], or venous invasion [8]. Primary tumour location also appears important, but this may not be for solely anatomical reasons. A primary tumour in the rectum, which is predominantly outside the peritoneal cavity, has a lower risk of pmCRC [9, 10]; but so too, a primary tumour of the rectosigmoid and sigmoid colon, which are within the peritoneal cavity [10]. While reports differ as to the relative risk of left or right colon primary tumour, even if adjusted for other factors such as pT stage [9, 12].

Risk factors for synchronous pmCRC are reported to be similar as those described above [4, 12].

4 Clinical symptoms & diagnosis

Peritoneal metastases can be asymptomatic, but symptoms most commonly include abdominal distention (with or without ascites), discomfort or pain, anorexia, breathlessness, and fatigue. The commonest critical complication of pmCRC is intestinal obstruction [15].

Computed tomography (CT) is the usual mode of diagnosis, but lacks sensitivity to detect small metastases and accuracy to determine the size of individual peritoneal metastases [16]. Laparoscopy is invasive but allows direct visualization of the peritoneal tumour burden and allows for histological diagnosis. Laparoscopy is used routinely for preoperative staging of gastric cancer [17, 18]; however, it is not routine for CRC, either preoperatively or during follow-up [19].

5 Prognosis

The prognosis for patients with pmCRC, with or without additional non-peritoneal metastatic sites, is generally worse than for patients with exclusively non-peritoneal mCRC [2-4]. Studies of patients with pmCRC have reported median OS durations in the range 12.0-18.8 months with systemic drug therapy [2], and 6 months without [8]. A meta-analysis of 14 randomised trials involving 10,553 mCRC patients, 1374 (13%) of whom had peritoneal metastases, reported mCRC patients with peritoneal-only metastases had shorter survival than those with a single (isolated) non-peritoneal site when treated with systemic treatment (median OS 16.3 vs 20.0 months respectively, HR=1.42[1.21-1.66], p<0.0001). Similarly, for patients with more than one site of metastasis, survival was worse if the peritoneum was included, with median OS of 12.6 months compared to 20.0 months for isolated non-peritoneal metastases (HR=1.79[1.67-1.93], p<0.0001). For patients with multiple metastases sites not including the peritoneum the OS was 15.7 months (HR=1.37[1.30-1.44], p<0.0001, isolated non-peritoneal metastases taken as reference) [2]. This observation appeared not to be explained by reduced use of chemotherapy or increased treatment related toxicity in pmCRC patients [3].

6 Biology

6.1 Pathophysiology

Understanding the evolution of mCRC involving the peritoneum is important when considering novel management strategies: Lemoine describes a step-wise evolution in detail [20]. Firstly, cancer cells detach from the primary colorectal tumour by spontaneous shedding through the bowel wall, increased intestinal fluid pressure, or by inadvertent spread as a result of surgery (**Figure 1**)**.** Detached cancer cells are then transported by the peritoneal fluid that rotates clockwise from the pelvis to the paracolic

gutter, sub diaphragmatic space and back to pelvis. The direction of the peritoneal fluid and the site of the primary tumour are thought to largely determine the site of peritoneal metastases. Cancer cells then attach to the mesothelial cells or the submesothelial lymphatics of the peritoneum by a cascade of molecular interactions. Attachment to the submesothelial lymphatics can facilitate translymphatic dissemination. Next, the cancers cells invade the subperitoneal space, then finally tumour angiogenesis provides the cancer cells with nutrition and oxygen for further growth and metastasis [20].

6.2 Molecular biology

It is increasingly understood that CRC cannot be considered as one disease. There are several proposed molecular classifications of CRC, including presence or absence of driver mutations (e.g. RAS, BRAF) [21], microsatellite instability status (MSI) [21], consensus molecular subtype (CMS) [22] and CRC intrinsic subtypes (CRIS) [23]. However, relatively little is known about the relationship between these molecular characteristics and the propensity to metastasise to the peritoneum or other specific sites. A study of 2563 mCRC patients with known BRAF mutation status indicated an association with BRAF status and peritoneal metastases: the primary tumour BRAF mutation rate was 18% in patients with peritoneal only-metastases; 12% in multi-organ including peritoneal metastases; 9% in non-peritoneal metastases (p=0.028) [2]. This finding is confirmed in two other studies, including 626 mCRC patients and 264 mCRC patients [24, 25]. Besides that, previous research has reported associations between BRAF status and right-sided CRC tumours [26], and between right-sided tumours and an advanced primary tumour [27]. Therefore, future research should investigate whether BRAF, site, advanced stage or a combination of those factors play a (key) role in the development of pmCRC. However, no significant association was found with

KRAS mutations (p=0.22 [2]; p=0.42 [24]), PIK3CA mutation (p=0.76 [24]) or MSI (p-value not given [28]).

7 Interventions for patients with peritoneal metastases

7.1 Risk reduction and earlier detection

Early detection of metachronous pmCRC is challenging as standard imaging with CT or PET have poor sensitivity for low-volume peritoneal metastases; but second-look surgery, although sensitive, is invasive and expensive. The Researchers at the Karolinska Institute used Swedish registry data to develop a model to identify those at high-risk of developing metachronous peritoneal metastases after curative resection of the primary tumour and whom may be best candidates for second-look surgery [29]. From a population of 8,044 stage I-III CRC patients, separate models were constructed for colon cancer and rectal cancer. Both models include clinical and histopathological characteristics to predict the 1-, 3-, 5-year probabilities of developing peritoneal metastases [30]. This was externally validated in a more recent population, which also showed that the model could be improved by adding subclasses of pT3 and pT4, and mucinous tumour histology [31].

Strategies to reduce the risk of development of incurable peritoneal relapse following curative CRC surgery include directed surveillance programs or preventative interventions following surgery. In a non-randomised study, 41 patients deemed as high-risk for peritoneal relapse underwent second-look surgery 12 months after their original resection. At this point 23/41 (56%) had visible peritoneal metastases, and were then managed with cytoreductive surgery (CRS, see section 7.2.2). All patients, including those without visible peritoneal metastases, received hyperthermic

intraperitoneal chemotherapy (HIPEC, see section 7.2.3.1). The 5-year OS rate was 90% [32].

Two randomized clinical trials (RCTs) investigated the role of active second look surgery with HIPEC as a prophylactic strategy to identify/prevent early peritoneal metastasis in high-risk CRC patients [33, 34]. PROPHYLOCHIP (NTC01226394) randomized 150 patients with synchronous peritoneal metastasis resected at the time of primary surgery, or history of ovarian metastases, or perforated primary tumour between second look laparotomy at six months with HIPEC versus routine surveillance only. All patients received systemic chemotherapy. In those that underwent second look laparotomy, peritoneal metastasis was diagnosed in 52%. Additional Clavien-Dindo complications grade 3-4 occurred in 41%. The 3-year disease-free survival (DFS) of 44% vs 51% and OS of 79% vs 80% was similar in the second look and surveillance group respectively. The authors conclude that a pro-active approach with second look and HIPEC offers no benefit compared to adequate surveillance [33]. Similarly, the COLOPEC study (NCT02231086) investigated the role of upfront HIPEC in those patients at high risk of recurrence. 204 patients with clinical or pathological T4N0–2M0-stage tumours or perforated colon cancer were randomly assigned before resection of the primary tumour, to adjuvant HIPEC simultaneously or within 8 weeks followed by routine adjuvant systemic chemotherapy or to adjuvant systemic chemotherapy alone. In the absence of recurrent disease all patients underwent laparoscopy at 18 months to detect peritoneal metastasis. There was no difference in peritoneal-free survival at 18-months for the experimental group (81%) vs the control group (76%) [34]. Results from both RCTs, PROHYLOCHIP and COLOPEC, suggest that prophylactic HIPEC is not beneficial for high-risk CRC patients [33, 34]. Another ongoing RCT investigates second and third look surgery (NCT03413254, **Table 1**).

7.2 Treatment of established peritoneal disease

The treatment of mCRC is multimodality and involves a multi-disciplinary team (MDT). A key role of the MDT is to consider which patients may benefit from localised management of metastatic disease, such as resection, ablation or regional drug therapy [35]. For most patients, however, the mainstay of treatment will be systemic drug therapy together with symptomatic and psychosocial palliative care [35].

7.2.1 Systemic treatment

The treatment pathway of established pmCRC treated with loco-regional therapy will usually include systemic chemotherapy to improve chances of long term disease control. For patients who have disease that is deemed too extensive for surgical intervention, systemic chemotherapy will be the backbone of their management, if deemed appropriate. A detailed review has been performed recently by Franko [36].

First-line systemic drug therapy for mCRC most commonly consist of a cytotoxic 'doublet' (FOLFOX [fluorouracil/oxaliplatin]; FOLFIRI [fluorouracil/irinotecan]; or CAPOX [capecitabine/oxaliplatin]), or a triplet regimen (e.g., FOLFOXIRI [fluorouracil/ oxaliplatin/irinotecan]) [35]. In combination with cytotoxic agents a therapeutic monoclonal antibody targeting vascular endothelial growth factor (VEGF) (bevacizumab) [37-39]; or aflibercept [35]), multi-kinase inhibitor (regorafenib [35]), or epidermal growth factor receptor (EGFR) (panitumumab [40]; or cetuximab [41]) if RAS wild-type. Most patients receive two or more 'lines' of therapy with these agents in sequence, interspersed with planned treatment breaks or periods on lower-intensity maintenance therapy. There remains some uncertainty around the selection and sequencing of these agents to achieve optimum duration and quality of survival, and health economic benefit; current practice is reviewed in detail in the European Society for Medical Oncology (ESMO) guidelines [35].

There is little published data on the efficacy of chemotherapy specifically in patients with peritoneal metastases. In a meta-analysis, patients with pmCRC were reported to have a worse prognosis with systemic treatment than patients without pmCRC (see section 5. Prognosis) [2]. Patients with peritoneal metastases in the CAIRO1/CAIRO 2 studies (n=81) had inferior median OS but received the same number of chemotherapy cycles as patients without pmCRC. There was an increase in major toxicity experienced in pmCRC patients, although not sufficient to stop treatment. The authors concluded that chemotherapy was less effective in pmCRC patients [3]. However, it remains uncertain whether this is due to decreased responsiveness to chemotherapy, resistance, undertreatment, or inherent features of peritoneal metastases [2]. It has been suggested that the dense extracellular matrix of peritoneal metastases may lead to diminished drug bio-availability and amplified drug clearance [36]. There may also be heterogeneity amongst histological sub-types: mucinous tumours are less likely to respond to systemic therapies than non-mucinous [42]. However pmCRC have a survival benefit from chemotherapy compared with best supportive treatment: pmCRC patients treated with chemotherapy had an OS of 12 months when treated with combination chemotherapy (irinotecan or oxaliplatin based) compared with 5 months with best supportive care [43].

Therefore research into the optimal systemic strategies for pmCRC patients is critical to improving outcomes for pmCRC patients. Currently, two RCTs are investigating systemic treatment specifically in pmCRC patients: one investigates the addition of bevacizumab to the FOLFOXIRI regimen (NCT02591667); the other tests the combination of oxaliplatin with either capecitabine or an alternative oral fluoropyrimidine, S-1 (NCT02870153) (**Table 1**).

7.2.2 Surgical treatment

“Cytoreductive Surgery” (CRS), was first described by John Spratt in 1980 for pseudomyxoma peritonei [44] and later by Paul Sugarbaker in 1995 for peritoneal metastases [45]. CRS denotes a surgical procedure to remove macroscopically visible peritoneal metastases through a combination of peritonectomy and organ resections [45], often followed by intraoperative peritoneal chemotherapy (see section 7.2.3) and systemic treatment (see section 7.2.1) [46]. In the years since its first description, there has been debate about the value of CRS for patients with pmCRC, and the selection of patients who may benefit.

Several different scoring systems have been proposed to assess patients’ suitability for CRS [47], of which ESMO guidelines recommend the Peritoneal Cancer Index (PCI) staging system [35]. PCI is based on the maximum diameter of peritoneal metastases in each of 13 anatomic zones. Within each zone, absence of metastases is scored as 0 and a score of 1, 2 or 3 is given if the largest metastasis is <0.5cm, 0.5-5.0cm or >5.0cm respectively. The PCI is calculated by adding the scores of all 13 regions with a maximum score of 39 [47]. CRS is recommended for patients with a PCI score <15 provided the lower ileal zone (area 12) is not involved. A PCI score of 15-20, or PCI <15 but with area 12 involvement, is a relative contraindication to CRS, and the procedure is definitely contraindicated in more advanced disease [48].

The importance of careful staging and patient selection for CRS has been highlighted in a recent meta-analysis of 2,838 pmCRC patients in 27 studies showing correlation between the completeness of cytoreduction and survival [49]. This confirms the poor survival of patients who undergo CRS but achieve only incomplete cytoreduction, underlining the importance of careful staging to avoid operating on such patients.

7.2.3 Intraperitoneal chemotherapy

The peritoneal cavity is a feasible route for drug delivery, with the potential to achieve higher drug exposure than with standard systemic administration, making intraperitoneal (IP) chemotherapy an attractive approach. Three different types of IP treatment have been studied: hyperthermic IP chemotherapy (HIPEC), early postoperative IP chemotherapy (EPIC) and sequential postoperative IP chemotherapy (SPIC) [46].

7.2.3.1 Hyperthermic intraperitoneal chemotherapy (HIPEC)

HIPEC is predicated on the observation that for a range of cytotoxic drugs, the cytotoxic activity and the penetration into cancer cells in vitro is increased in conditions of mild hyperthermia [50]. The procedure was developed as an adjunct to CRS and is shown in **Figure 2** and **Table 2**. Immediately following the CRS procedure, heated chemotherapy is pumped into the peritoneum and recirculated, maintaining a constant IP temperature around 41-43 ℃ for 30 to 90 minutes, then drained before closure of the abdomen [50]. HIPEC is often combined with (adjuvant) systemic treatments (see section 7.2.1 for systemic treatment) [51-67].

HIPEC was initially developed using mitomycin C, and subsequently with oxaliplatin, cisplatin, irinotecan and 5-fluorouracil (FU) either as single agents or in combinations [52-56, 58-60, 63, 68-74]. A recent study showed similar rates of post-operative complications and medium-term efficacy outcomes following HIPEC with either a 90-minute exposure to mitomycin C or a 30-minute exposure to oxaliplatin [51].

The use of CRS/HIPEC in pmCRC patients has been reported in over 17 large (>100 patients) retrospective series [52, 53, 56-65, 68-75]. These non-randomised studies, though not providing interpretable information about efficacy compared with CRS

alone, showed that CRS/HIPEC morbidity is in the range 22-53% and treatment-related mortality 0.7%-4.6% [52-54, 56, 58, 60-63, 69-71, 74]. Serious complications include abdominal infections [62, 69, 70, 74], anastomotic leaks [61, 69, 74], fistula [52, 69, 70, 72], and neutropenia/thrombocytopenia [58, 69, 70, 72]. Higher complication rates are associated with poor performance status, higher PCI score, longer surgery, number of anastomoses, extent of cytoreduction and dose of chemotherapy.

Only one small Dutch RCT has been reported comparing CRS/HIPEC to non-surgical treatment. 105 pmCRC patients were randomised to systemic FU plus folinic acid (FU/FA) alone or CRS/HIPEC with mitomycin C followed by systemic FU/FA. Median progression-free survival (PFS) was 12.6 months with CRS/HIPEC and 7.7 months in the control arm (p=0.02). The disease specific survival was 22.2 months with CRS/HIPEC and 12.6 months for patients treated with only systemic chemotherapy (p=0.028) [54, 55].

One of the criticisms on the Dutch RCT was that they did not use modern systemic chemotherapeutics such as oxaliplatin and irinotecan. Two retrospective case-control studies indicated that the median OS was significantly longer with CRS+HIPEC+SC compared to modern SC alone (Elias et all 62.7 vs 23.9 months, $p<0.05$; Franko et all 34,7 vs 16.8 months, $p<0.001$). [64, 65]. These results suggest that the addition of CRS+HIPEC could even be beneficial in the modern chemotherapy era.

The recently reported PRODIGE 7 trial (NCT00769405) [66, 67] is the only phase III RCT to date to have evaluated the addition of HIPEC to CRS. 265 patients with isolated pmCRC were randomized between CRS alone or CRS plus oxaliplatin-based HIPEC. There was no evidence of benefit from HIPEC: the median OS was 41.2 months with CRS versus 41.7 months with CRS/HIPEC (HR=1.00[0.73-49.7],p=0.99); relapse-free survival was 11.1 versus 13.1 months (HR=0.90[0.69-1.90] p=0.49). CRS/HIPEC

produced greater 60-day morbidity compared with CRS alone (24.1% vs 13.1%, p=0.030), but 30-day mortality, at 1.5%, was equal in both arms [66]. Exploratory subgroup analysis suggested a possible benefit of HIPEC confined to patients with more extensive disease PCI 11-15 [67].

The 2016 ESMO guideline recommends CRS/HIPEC as a treatment for pmCRC patients [35], but this predates the reporting of PRODIGE-7 [66, 67]. HIPEC with or without CRS or other treatments is currently investigated in six ongoing clinical trials involving CRC patients at high-risk of developing peritoneal metastases, and twelve clinical trials involving patients with established pmCRC (**Table 1**) ; clinicians should consider using CRS with or without HIPEC pending the results of these studies. CRS, with or without HIPEC, is limited to specialised centres (e.g., just three approved to serve the UK population of 65M), leading inevitably to variability in patient identification and referral from non-specialist units. The procedure is now also being evaluated in patients with peritoneal metastases of gastric [17] and ovarian cancer [76], which will potentially require an expansion of the service to meet growing demand.

7.2.3.2 Early post-operative intraperitoneal chemotherapy (EPIC)

Developed as an alternative to HIPEC, EPIC involves leaving one or more transcutaneous peritoneal catheters in place after surgery (**Figure 2** and **Table 2**). The next day, chemotherapy dissolved in peritoneal dialysis fluid is infused at room temperature, retained in the abdomen for up to 24 hours, then drained. This procedure is repeated for up to six days post-surgery. After the last drainage the catheters are removed [77-79].

Two RCTs have evaluated the efficacy of EPIC after surgery for CRC with peritoneal involvement, but both were terminated early. The first compared EPIC plus systemic

FU/FA versus observation alone. Recruitment stopped, with 267 patients randomised, when the efficacy of adjuvant systemic chemotherapy was confirmed from other trials; no statistical benefit was seen in DFS or OS (p=0.26 and p=0.30, respectively) [78]. The second trial compared post-operative systemic chemotherapy with or without EPIC, but closed early due to poor recruitment with only 35 patients randomised; again, no survival benefit was seen [80]. Currently, a further randomised phase II RCT is investigating the DFS of post-operative EPIC compared with HIPEC (NCT01815359), and one observational clinical trial investigates the quality of life after HIPEC or EPIC (NCT03503071) (**Table 1**).

In a retrospective report of 52 CRC patients (including 16 with metastatic CRC) with positive peritoneal lavage but no radiological evidence of peritoneal metastases, 31 patients received mitomycin C EPIC following surgery, while 21 had surgery alone. With the caveats of a non-randomised comparison, the EPIC group reported better peritoneal recurrence-free and cancer-specific survival (p=0.0003 and p=0.0001 respectively). EPIC was well tolerated: one patient (1.9%) had catheter-related skin ulceration but no other serious complications were reported [81]. In another single-centre case-control study of 45 patients with pmCRC, comparing CRS with or without EPIC, patients treated with EPIC were noted to have better OS and DFS with no increase in morbidity or mortality [77]. A further series suggests that laparoscopic resection with EPIC is a safe alternative to open surgery [79].

7.2.3.3 Sequential post-operative intraperitoneal chemotherapy (SPIC)

SPIC is a further variant of IP therapy which, like EPIC, involves catheter placement during primary cancer resection or CRS, but with the IP chemotherapy then delivered over several week or months (**Figure 2** and **Table 2**) [46]. There are three studies of

SPIC in CRC patients to date. A phase Ib frequency-escalation trial in 51 patients assessed the safety and feasibility of giving IP FU/FA in icodextrin-based dialysis fluid, alongside standard weekly intravenous (IV) adjuvant FU/FA, following resection of primary CRC. The frequency of IP administration was escalated in cohorts from 4-weekly to 3-weekly, 2-weekly, and finally weekly. The maximum tolerable frequency of IP administration was determined to be 2-weekly. Pharmacokinetic analysis showed >100-fold fluorouracil exposure (area under the concentration/time curve) for IP compared with IV administration. In this study a subcutaneous port catheter system ("Portacath") was used, but 20% patients experienced a technical failure of the IP catheter: blockage, leakage, pain or infection, and one patient experienced a bowel perforation [82]. Another study randomized 48 pmCRC patients between CRS+SPIC or systemic chemotherapy only, but closed early due to poor recruitment. IP FU/FA was administered daily for 6 days using a Portacath, with repetitions every 4-6 weeks to 6 months post-operative. Systemic treatment consisted of 12 cycles of biweekly FOLFOX-6. Results suggested a survival benefit for the CRS+SPIC group; median OS of 25 months with CRS+SPIC versus 18 months with systemic chemotherapy only (HR=0.51[0.27-0.96], p=0.04) [83].

A retrospective report of 151 pmCRC patients compared "open-and-close" surgery (n=23), CRS+HIPEC (n=69) and CRS+SPIC (n=57). Again, SPIC was delivered using a Portacath, but the schedule was daily for 6 days, repeated every 4-6 weeks out to 6 months post-operative. In this non-randomised study, the CRS+SPIC patients had median OS of 25 months with a 5-year survival of 18%, while the CRS+HIPEC group had median OS of 34 months [59].

Data for SPIC in pmCRC patients is limited and there are no ongoing RCTs. However, SPIC is more extensively studied in other cancers: in ovarian cancer has been

demonstrated to improve outcomes [84, 85], while results in gastric cancer are inconsistent [86, 87].

7.2.4 Experimental treatments

One problem with EPIC and SPIC is that the distribution of IP fluid, and therefore chemotherapy, to the entire peritoneal surface may be unreliable. An experimental delivery called “pressurized intraperitoneal aerosol chemotherapy” (PIPAC) is also undergoing investigation in pmCRC patients. With PIPAC, chemotherapy is delivered into the inflated peritoneal cavity during laparoscopy as a pressurised aerosol. The technique was developed in pigs using a test dye, and appeared to give better distribution than the same dye delivered in a fluid medium [88]. Early clinical studies of PIPAC in patients with peritoneal metastases of gastric [89] and ovarian cancer [90] showed promising data in terms of safety and microscopic tumour responses (defined by the absence or presence of tumour cells). PIPAC with oxaliplatin has been reported in a study of 17 pmCRC patients, of whom four experienced grade III adverse effects. The median OS after the first PIPAC treatment was 15.7 months, and 71% of all biopsies had microscopic tumour responses after two cycles of PIPAC [91]. Currently, four ongoing phase II or III RCTs investigate the application of PIPAC in patients with pmCRC, or in CRC patients who have a high-risk to develop peritoneal metastases (**Table 1**).

The peritoneum may also be considered as a route of administration for novel anticancer agents. For example MOC31PE is a monoclonal antibody targeting the EpCAM adhesion molecule, conjugated to Pseudomonas exotoxin A. In a phase I study which included 17 pmCRC patients, MOC31PE was delivered IP the day after

CRS/HIPEC. The approach appears safety and tolerable, with minimal systemic drug uptake [92].

8 Conclusion

Metastasis to the peritoneum is a common feature of colorectal cancer but poses many therapeutic challenges. [7, 8]. Detection of peritoneal metastases is difficult as they may be asymptomatic or cause non-specific symptoms [15], and because routine follow up screening with modalities such as CT scanning have low sensitivity for peritoneal metastases [16]. Individual risk assessment models may however help by predicting the risk of metachronous peritoneal metastases after curative resection [29, 31]. Future studies will be required to further validate and optimize the risk models published by Segelman et al [29], and develop a suitable surveillance program for high-risk patients.

The treatment of established pmCRC requires careful patient assessment and specialist multidisciplinary input. If active treatment is indicated, it is often multi-modality with systemic therapy and loco-regional approaches. Despite advances in chemotherapy and targeted therapy, the OS of patients with peritoneal metastases is poor [2-5], and significantly shorter than that of patients with non-peritoneal metastases [2]. Loco-regional treatment for established peritoneal metastases has centred on combinations of CRS and IP drug therapy, but there have been few well-powered RCTs conducted to date. We have reviewed several approaches to delivering IP drug therapy (HIPEC [54, 55]; EPIC [77, 81]; SPIC [59, 82]; PIPAC [91]). Of these, EPIC is relatively quick and avoids the need for specialized equipment; however, its efficacy has yet to be proven in RCTs. HIPEC, although requiring specialist facilities, has been extensively studied as an adjunct to CRS [52-63, 68-75]; however, the recent PRODIGE 7 trial suggest that the benefits seen in previous non-randomised trials may

have been due to CRS rather than HIPEC [66, 67]. Further randomised trials are needed to establish whether IP therapy truly improves outcomes for patients undergoing CRS for established pmCRC. If so, optimising the treatment delivery technique and drugs used will help bring these modalities into standard care. Lastly, it will be important to investigate the optimal timing, sequencing and combination of the various systemic, surgical, and intraperitoneal therapies.

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Tables

Table 1: Active clinical trials involving colorectal cancer patients at high-risk of developing peritoneal metastases or patients with established peritoneal metastases. Information was retrieved from *ClinicalTrials.gov, by searching for 'condition or disease: peritoneal metastases' and 'condition or disease: colorectal cancer, Other terms: intraperitoneal chemotherapy'. Studies all recruited CRC with high*-risk profile for developing peritoneal metastases, or established synchronous or metachronous peritoneal metastases. Studies may also recruited other cancer types with high-risk profiles or established peritoneal metastases. All studies had primary completion and/or study completion dates in the future. Last assessed on 31-01-2019.

Intervention		Population of CRC patients in respect to peritoneal metastases status	Study type	Phase	NCT identifier
Second/third look laparoscopy		High-risk	Intervention	III	NCT03413254
Systemic therapy		Established	Intervention	II	NCT02591667 NCT02870153
HIPEC		High-risk	Intervention	II	NCT02830139;
				III	NCT02179489; NCT02614534; NCT02965248; NCT02974556; NCT03221608
		Established	Intervention	I	NCT03732781
				II	NCT02040142; NCT03073694
				N.A.	NCT03398512
			Observation	N.A.	NCT02082886; NCT02754115; NCT03604653; NCT03733184
	+/- perioperative systemic chemotherapy	Established	Intervention	II/III	NCT02758951
	+/-perioperative administration of dexmedetomidine	Established	Intervention	N.A.	NCT03370588
HIPEC or EPIC		Established	Observation	N.A.	NCT03503071
			Intervention	II	NCT01815359
PIPAC		High-risk	Intervention	II	NCT03280511
		Established	Intervention	II	NCT03287375
				II-III	NCT03246321; NCT03294252
Intra-peritoneal chemotherapy (not specified as HIPEC, EPIC, PIPAC)		High-risk	Intervention	N.A.	NCT03561948
		Established	Intervention	I	NCT02833753
				II	NCT02399410; NCT03792269
Other	Immunotherapy	Established	Intervention	I-II	NCT03757858
	CAR-T	Established	Intervention	I	NCT03682744

CAR-T= chimeric antigen receptor on T cells ; CRC= colorectal cancer; EPIC= early postoperative intraperitoneal chemotherapy; HIPEC= hyperthermic intraperitoneal chemotherapy; N.A.= not applicable; NCT = national clinical trial; PIPAC= pressurized intraperitoneal chemotherapy.

Table 2: **Key differences between the three intraperitoneal chemotherapy modalities.** Hyperthermic intraperitoneal chemotherapy (HIPEC), early post-operative chemotherapy (EPIC), or sequential post-operative chemotherapy (SPIC).

	HIPEC	**EPIC**	**SPIC**
When is the chemotherapy given?	During surgery	Postoperative	Postoperative
How long is it given?	On day of surgery, given for 30-90 minutes	Once every day for day 1 till day 4 or 6 postoperative	Sequential doses over several weeks or months
Temperature	Heated (41-43 ℃)	Normothermic (37 ℃)	Normothermic (37 ℃)

Figures

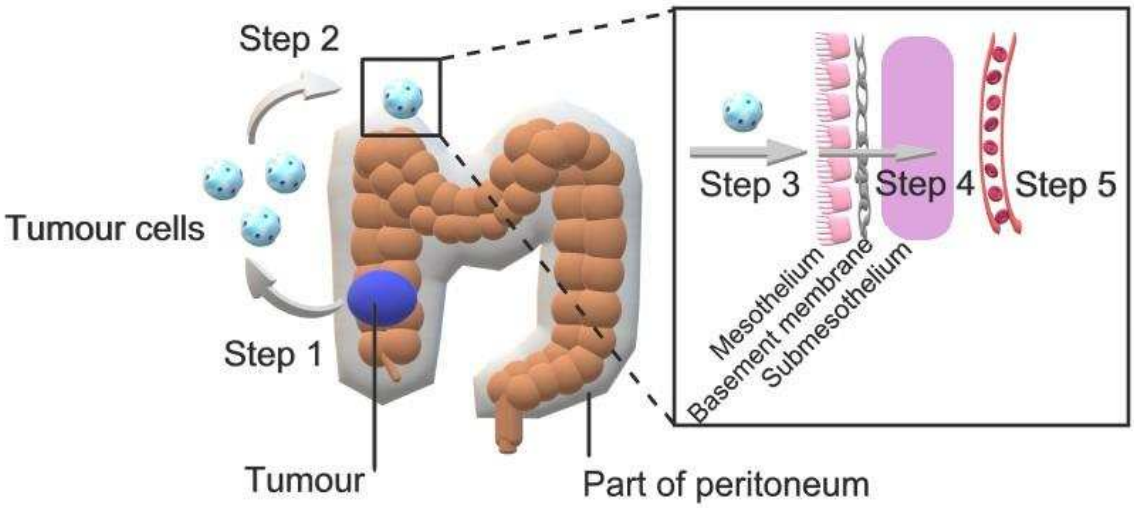

Figure 1 (colour in print and online)

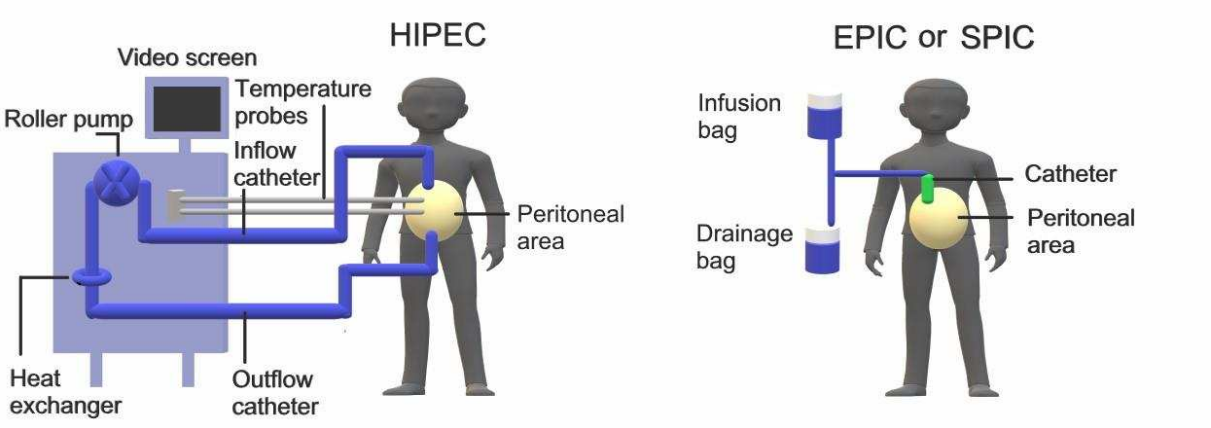

Figure 2 (colour in print and online)

Figure 1: Pathophysiology of peritoneal metastases of colorectal cancer.

Step 1: Shedding of tumour cells from the primary colorectal tumour. Step 2: Transport of the tumour cells by the peritoneal fluid in the direction of the white arrows. Step 3: tumour cells attach to the peritoneum by attaching to mesothelial cells in the mesothelium or by transport through the submesothelial lymphatics. Step 4: Invasion of the submesothelium. Step 5: Angiogenesis. This figure is based on the information and figures of Lemoine et al. [20]

Figure 2: Illustration of the three intraperitoneal chemotherapy modalities. Hyperthermic intraperitoneal chemotherapy (HIPEC), early post-operative chemotherapy (EPIC), or sequential postoperative chemotherapy (SPIC). This figure is partly inspired from : http://kianous-stavros.gr/en/cytoreductive-surgery-hipec/