Colorectal peritoneal metastases-Pathogenesis, diagnosis and treatment options: an evidence based update

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.15796](https://doi.org/10.1111/ans.15796)

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This manuscript has 4661 words (including abstract, manuscript and references) and contains 1 figure, 2 supplementary figures and 1 supplementary table.

Key words: peritoneal disease, cytoreductive surgery, HIPEC

Conflicts of interest and disclosures: The Authors have no disclosures or conflicts of interest.

Abstract

Peritoneal metastases confer the worst survival amongst all sites in patients with metastatic colorectal cancer. They develop largely through transcoelomic spread, with a sequence of events that allows cells to firstly detach from primary tumours, survive in the peritoneal environment, attach to the peritoneal surface of organs and migrate into the submesothelial space to create a microenvironment conducive to metastatic growth. Diagnostic challenges have previously hindered early identification of peritoneal metastases. While advances in diagnostic modalities have improved our ability to identify peritoneal metastases, lesions under 0.5 cm remain challenging to detect. The advent of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can offer selected patients with colorectal peritoneal metastases a favourable long-term survival. Recent trials however, have cast doubts on the efficacy of HIPEC, with the recent PRODIGE 7 trial showing no benefit from oxaliplatin based HIPEC in addition to good quality CRS in resectable disease. While peritoneal recurrence can be reliably predicted from high-risk features in primary tumours such as a perforated cancer, ovarian metastases or T4a cancers, the use of prophylactic second look surgery with HIPEC or adjuvant HIPEC failed to demonstrate any survival benefit in high risk cases in recent clinical trials, raising further questions about the efficacy of HIPEC. With high failure rates from systemic chemotherapy in unresectable disease, novel surgical techniques such as pressurised aerolised chemotherapy (PIPAC) are being investigated in clinical trials worldwide. Further collaborative research is needed to explore newer avenues of treatment for this poor prognostic cohort.

Peritoneal metastases (PM)

The peritoneum is the third most common site for metastases, but confers the worst prognosis in patients with metastatic colorectal cancer.¹ Synchronous PM are seen in 4-13% of patients,^{1, 2} with metachronous disease in up to 19% of patients.³ Approximately 30-40% of patients with colorectal cancer develop PM at some point during their surveillance and follow-up^{1, 4}, with the peritoneum the only site for metastases in 41%.³ Historically, PM were viewed with nihilism, with a median survival of only three to six months.⁵ Today, this is no longer the case, with improvements in treatment options. This review aims to update all clinicians about the pathogenesis, risk factors, diagnosis and treatment options for PM from CRC.

Literature Search

A literature search of PubMed and MEDLINE was performed from 2000 onwards, with a focus on original research, clinical trials, review articles and meta-analyses on colorectal peritoneal metastases (CRPM).

Pathogenesis of peritoneal metastases

The peritoneum is a fertile site for metastases to develop largely because of its extensive surface area. The development of PM is based on the “tumour cell entrapment” hypothesis⁶ (Figure 1).

1) Cancer cells detach from the primary tumour.

The risk factors for primary tumours shedding cancer cells into the peritoneal cavity, and thus the development of peritoneal metastases includes serosal invasion (T4a), perforated cancers, and positive resection margins. Shedding of cancer cells occur due to high interstitial fluid pressure within tumours together with inefficient lymphatic drainage.⁷

During this process, cancer cells undergo epithelial to mesenchymal transformation (EMT) (Figure 1a), involving loss of cell polarity, degradation of cell-cell junctions, changes in the cytoskeleton and loss of membrane glycoproteins, notably E-Cadherin. E-Cadherin normally suppresses cell motility, invasion and metastasis. EMT is considered to be a key step in initiation of local invasion and subsequent dissemination.⁸

2) Cancer cells develop the ability to survive in the peritoneal environment.

Epithelial cells normally undergo programmed cell death when they lose attachment to the extracellular matrix (ECM), a phenomenon called anoikis. Tumour cells are resistant to anoikis, thereby being able to survive as circulating tumour cells (CTCs).⁸ Dissemination of cancer cells is facilitated by normal peristaltic movements of the bowel. Furthermore, cancer cells can increase motility through activating actin microfilaments on their membrane surface.⁹

3) Cancer cells adhere to the peritoneum.

While CTCs can theoretically go to any site, they deposit preferentially at certain sites due to a pre-existing metastatic niche. Coined by Paget¹⁰ as the “soil and seed hypothesis”, it suggests that cancer cells can only grow in certain microenvironments. While the peritoneal cavity is large, the greater omentum is one of the most common sites for metastases. Gerber et al¹¹ showed this was because of the presence of ‘milky spots’; aggregates of immune cells with large numbers of macrophages, with high vascular density and active angiogenesis, creating an environment highly favourable for tumour cell growth.

Cancer cells express surface proteins such as integrins, which can adhere to components of the ECM such as collagen, laminin, and fibronectin (Figure 1b). Mesothelial cells express a number of adhesion molecules such as intercellular (ICAM-1), vascular (VCAM-1) and platelet endothelial cell adhesion molecules (PECAM-1). Mesothelial cells assist adhesion of cancer cells to the peritoneum through interaction of CD44, a surface ligand on cancer cells with ICAM-1 on the surface of mesothelial cells.¹² The binding of mesothelial cells to integrins on cancer cells

upregulates production of pro-inflammatory mediators such as IL-1 β , IL-6, and TNF- α ,¹³ with the submesothelial stroma providing necessary mediators that allow cell survival, proliferation and invasion.

4) Cells migrate and gain access to the submesothelial space.

The submesothelial stroma is largely composed of fibroblasts that secrete structural proteins including collagen, fibronectin and elastin.¹² This tissue between the mesothelial cell layer and the submesothelial capillaries is also designated as the peritoneal-blood barrier, which generally does not permit movement of nutrients and oxygen from capillaries to the peritoneal cavity. This ensures that most cancer cells that attach to the mesothelial layer die off.¹⁴ However, once cells adhere to the peritoneum with adhesion molecules like CD44, they can gain access to the submesothelial space via a chemotactic gradient generated by stimuli released by mesothelial cells, fibroblasts and adipocytes.¹² They can also gain entry to the submesothelial space in areas of peritoneal discontinuity from prior peritoneal injury or trauma.⁷ Additionally, cancer cells can induce mesothelial cell apoptosis through Fas-dependent mechanisms (Figure 1c).¹⁵

Once cancer cells establish themselves in the submesothelial space, cancer associated fibroblasts (CAFs) support tumour growth and progression. Mesothelial cells can also undergo a mesenchymal to mesenchymal transition (MMT) switching to a CAF phenotype, rendering the peritoneum more receptive to tumour attachment.¹⁶ This transition may be dependent on TGF- β ₁.¹⁷ Peritoneal macrophages also assist tumour development by producing various angiogenesis factors including VEGF, MMP-1 and amphiregulin.¹²

5) Cells must be able to establish a supportive microenvironment.

Cancer cells can release factors that disrupt the peritoneal blood barrier, leading to neo-angiogenesis and creation of an immunosuppressive tumour microenvironment (Figure 1d). Once cancer cells have invaded the submesothelial stroma, the endothelial lining of the lymphatics and blood vessels in the stroma promote further cancer growth through

recruitment of monocytes and other immunosuppressive cells, supported by CAFs and peritoneal macrophages. Among their other functions, CAFs produce various cytokines, including VEGF and remodel the ECM to create a pro-tumorigenic environment facilitating tumour growth and proliferation. Cancer cells also release chemokines such as HMGB1, which promote neo-angiogenesis, and recruit macrophages and myeloid derived suppressor cells (MDSCs). Overall, these factors promote further tumour growth.

While transcoelomic spread is a more commonly appreciated method of peritoneal spread, haematogenous spread is also an important route. Here, CTCs travel first via draining lymph nodes to eventually reach the circulation. CTCs can develop the ability to leave the circulation through activating platelets and secretion of adenine nucleotides, which induce opening of the endothelial barrier, allowing CTCs to gain direct entry into the submesothelial space.¹⁸

Diagnosis of peritoneal metastases

There are no specific symptoms that suggest the presence of PM. Patients can be asymptomatic, while others may present with abdominal pain and distension, unintentional weight loss or cachexia, prompting further investigation. In most cases, PM are detected on staging or surveillance imaging or incidentally at time of surgery.

Common imaging modalities used in the diagnosis of peritoneal metastases include contrast-enhanced multi-detector computed tomography (CT), ¹⁸F-Fluorodeoxyglucose positron emission tomography (PET-CT), and diffusion-weighted magnetic resonance imaging (DW-MRI).

Classic imaging features that suggest high volume peritoneal disease include omental caking, scalloping of the liver or diaphragm, mucinous ascites and nodules >1 cm.¹⁹ Studies have found that CT scanning has limited sensitivity in detecting peritoneal nodules <0.5cm, with improved sensitivity with increased lesion size.²⁰ Furthermore, peritoneal carcinomatosis index (PCI) was significantly underestimated by radiological assessment compared to intraoperative PCI.

The combination of CT and DW-MRI offers a more accurate assessment of the PCI than CT alone.²¹ However, the overall accuracy of dual modality imaging was again dependent on volume of disease. Similar to other modalities, PET/CT has low sensitivity in the detection of nodules <1cm. However, PET/CT scans are helpful when MRI or CT have been inconclusive. Two recent meta-analyses found an overall diagnostic accuracy of 87-92% with PET/CT^{22,23}, suggesting that a hot spot found on PET/CT can be reliably assumed to be a peritoneal metastasis.

Limitations in imaging modalities have led to the use of staging laparoscopy as an adjunct to help evaluate disease burden. Many centres perform staging laparoscopies routinely before offering cytoreductive surgery. Laparoscopy has been shown to be helpful in identifying clearly unresectable patients, thereby avoiding a morbid laparotomy.^{24,25} However, despite laparoscopy and imaging modalities, some patients are still found to have unresectable disease at operation. This underlines the overall challenge in accurately staging and detecting peritoneal metastases.

A recent survey of the Peritoneal Surface Oncology Group International (PSOGI) found that most experts recommended only a CT scan as routine pre-operative staging, with the use of MRI, PET/CT and laparoscopy only when additional information was needed.²⁶

Treatment options

Patients with colorectal peritoneal metastases (CRPM) can be broadly divided into three distinct categories to stratify treatment options (Figure S1):

- 1) Resectable CRPM
- 2) Unresectable CRPM
- 3) Primary tumours at high risk for developing peritoneal metastases

Resectable CRPM: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)

Over two decades ago, an aggressive loco-regional treatment for peritoneal disease arose in the form of cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC).

Pioneered by Sugarbaker *et al*,²⁷ it involves removal of all macroscopic deposits of tumour within the peritoneal cavity. Chemotherapy, heated to 41-43°C, is then administered to the peritoneal cavity. HIPEC aims at delivering a higher concentration of chemotherapy intraperitoneally, whilst minimising systemic exposure and hence toxicity.²⁸ The hyperthermia works synergistically with chemotherapy to eradicate microscopic disease and free tumour cells.²⁹ In a randomised trial (RCT), Verwaal *et al*³⁰ showed that CRS with Mitomycin C based HIPEC nearly doubled the median survival compared to palliative systemic therapy (22.3 months vs 12.6 months). These survival differences remained significant at 8-year follow-up. This trial emphasised that CRPM is a surgical disease, with patients undergoing successful complete cytoreduction having a 48 months median survival, with a 45% five-year survival.³¹ Today, CRS and HIPEC performed at high-volume centres can offer selected patients with resectable CRPM a 19.2-34 months median overall survival (OS) with a 19-48% five-year survival.³²⁻³⁴ The key prognostic factors that impact on survival are the peritoneal carcinoma index (PCI) and the completeness of cytoreduction (CC score). The PCI is a measure of the burden of disease, while the CC score is a measure of residual disease remaining. The aim is always to achieve a CC-0 clearance, implying no residual visible disease. While CRS and HIPEC offers the best chance for long term survival to patients with low volume CRPM, it does carry a 17.6-52.4% risk of major morbidity, with a 0-8.1% risk of mortality.³⁵⁻³⁷

In recent years, CRS and HIPEC has been integrated into the treatment pathway guidelines in the management of low volume CRPM in many countries.^{38, 39} While CRS and HIPEC is utilised together, the recently reported PRODIGE 7 trial⁴⁰ has questioned the efficacy of HIPEC, specifically Oxaliplatin based HIPEC. This RCT demonstrated an impressive 41.2 months median overall survival following CRS alone. The addition of Oxaliplatin HIPEC did not offer any significant survival benefit, with those receiving HIPEC having a significantly increased

complication rate. Subgroup analysis however demonstrated a survival benefit with HIPEC only in patients with a PCI of 11-15. This trial has contributed to international debate on the role of HIPEC, with Oxaliplatin felt suboptimal as a HIPEC agent. Based on these results, it would appear logical to use only Mitomycin C, especially given the use of Mitomycin C HIPEC in conjunction with CRS is supported by randomised evidence.³⁰ To date, there are no prospective studies comparing the efficacy of different HIPEC agents.

Role of systemic chemotherapy in resectable CRPM

The role of peri-operative systemic chemotherapy in patients with resectable CRPM is variable around the world. In Netherlands, peri-operative systemic chemotherapy is not routinely used and patients with resectable CRPM undergo upfront CRS and HIPEC.⁴¹ In countries like France however, peri-operative systemic chemotherapy is routinely used alongside CRS and HIPEC.⁴⁰ It is noteworthy that the best results from CRS and HIPEC have been achieved in conjunction with the use of peri-operative systemic chemotherapy.^{40, 42} The use of neo-adjuvant chemotherapy may allow assessment of tumour biology, with adjuvant chemotherapy administered to treat residual micro-metastatic disease. Stand-alone systemic chemotherapy however, has no role as the mainstay of treatment in patients with resectable CRPM. The CAIRO6 RCT⁴¹ (NCT 02758951) is currently recruiting in Netherlands evaluating peri-operative systemic chemotherapy with CRS and HIPEC against upfront CRS and HIPEC. Results from this trial would help better define and standardise the role of peri-operative systemic chemotherapy.

Unresectable CRPM: Systemic Chemotherapy

Patients are deemed unresectable largely based on volume of disease. Studies have demonstrated that the benefit of curative intent CRS and HIPEC diminishes with a higher PCI, with five-year survival less than 10% in those with a PCI >20.³³ While five-year survival with systemic chemotherapy is only 4.1% in the setting of unresectable CRPM,⁴³ its lower morbidity compared to CRS and HIPEC makes it the mainstay of treatment for these patients. Not

surprisingly, disease progression and treatment failures are exceedingly common. Research into newer avenues of treatment are urgently needed for this cohort.

Unresectable CRPM: Novel techniques

In recent years, novel surgical techniques are emerging, directed at patients with unresectable CRPM. Pressurised intraperitoneal aerosolised chemotherapy (PIPAC) has been used in a number of centres as a palliative treatment in patients with unresectable CRPM to provide symptom control and improve quality of life (Figure S2). PIPAC is a laparoscopic technique that uses an aerosol delivery mechanism for chemotherapy, to ensure a more homogenous drug distribution throughout the peritoneum with better tissue penetration.⁴⁴ Early reports on the use of PIPAC are promising, showing it to be safe, with low toxicity, with objective tumour regression in selected patients.^{44, 45} Clinical trials are currently underway to evaluate the safety and feasibility of PIPAC in CRPM (NCT03868228, NCT03246321).

High risk patients with no evidence of CRPM on pre-operative assessment: Role of Early re-look, prophylactic HIPEC or adjuvant HIPEC

In approximately 25% of primary CRC resections, there are clinical or pathological findings that indicate a high risk for future PM⁴⁶ (Table S1). Studies have evaluated the role of a proactive approach in patients with high risk for developing peritoneal recurrence.

Elias *et al*⁴⁷ demonstrated that asymptomatic peritoneal metastases were diagnosed in 55% of cases undergoing a “proactive” second look laparotomy 13 months after resection of a high-risk primary cancer. These included resected synchronous PM, synchronous ovarian metastases and perforated primary tumours. In a follow-up study using this “proactive” approach, PM were found in 56% of patients undergoing second look surgery 12 months following high-risk primary tumour resection. Following successful CRS and HIPEC at second look surgery, five-year OS was 90%, with five-year disease-free survival (DFS) of 44%.⁴⁸

Two recently completed RCTs explored a proactive approach in high-risk patients. The ProphyloChip (NCT01226394) trial⁴⁹ compared early relook with CRS and Oxaliplatin HIPEC versus surveillance for asymptomatic patients at six months following resection of a high-risk primary tumour. While PM were found in 52% of patients undergoing second look surgery, there was no difference in three-year DFS or OS between the two arms. The COLOPEC trial (NCT02231086)⁵⁰ evaluated the role of adjuvant HIPEC after a high-risk primary tumour resection. This trial also failed to find a difference in peritoneal metastasis free survival with the use of adjuvant Oxaliplatin HIPEC. Despite optimism for a proactive approach to treating and preventing early peritoneal recurrence, two RCTs have now shown no benefit for such an approach over standard surveillance. It is possible that these negative results may be due to Oxaliplatin being a suboptimal HIPEC agent, with the HIPECT4 (NCT02614534) clinical trial currently exploring the role of Mitomycin C as adjuvant HIPEC in high-risk cases. At this stage, routine use of prophylactic or adjuvant Oxaliplatin HIPEC cannot be recommended outside of a clinical trial.

Conclusion

Peritoneal disease remains an underappreciated area, with very few clinical trials in the last two decades. PM is a surgical entity, with the greatest advance in the management of CRPM in recent times being adoption of CRS and HIPEC, that can offer selected patients with a favorable long-term survival. For those with unresectable disease, chemotherapy remains the mainstay of treatment. However, with innovative techniques such as PIPAC, and advances in translational research showing promise, there is hope on the horizon.

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Figure Legends

Figure 1. Sequence of events leading from cancer cells being shed from the primary tumour, to establishment of peritoneal metastases

VCAM-1, ICAM-1, PECAM-1: vascular, intercellular and platelet endothelial cell adhesion molecules; TGF- β : Transforming growth factor beta; CAF: cancer associated fibroblasts; M₁: M₁ macrophages: that are tumour suppressive; M₂: M₂ macrophages that are pro-tumourogenic; IL-4, IL-6: Interleukin 4 and 6; VEGF: Vascular endothelial growth factor; T-reg: T- regulatory cell; Th₁₇: subtype of CD4

Supporting Information

Figure S1. Treatment options for patients with colorectal peritoneal metastases

Figure S2. Laparoscopic view of colorectal peritoneal metastases on the left. Pressurised intraperitoneal aerosolised chemotherapy (PIPAC) delivery on the right with laparoscopic delivery of aerosolised particles of chemotherapy

Table S1. Table 1. Summary of risk factors for peritoneal recurrence

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Colorectal peritoneal metastases: pathogenesis, diagnosis and treatment options - an evidence-based update

Date:

2020-03-04

Citation:

Narasimhan, V., Ooi, G., Michael, M., Ramsay, R., Lynch, C. & Heriot, A. (2020). Colorectal peritoneal metastases: pathogenesis, diagnosis and treatment options - an evidence-based update. ANZ JOURNAL OF SURGERY, 90 (9), pp.1592-1597. <https://doi.org/10.1111/ans.15796>.

Persistent Link:

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