Clinical question: Peritonectomy with HIPEC

Background

Peritoneal metastases are present synchronously in 5–10% of patients at the time of diagnosis of primary colorectal cancer. They may also occur metachronously following treatment of the primary colorectal cancer. Because peritoneal carcinomatosis is associated with a poor prognosis, a conservative surgical approach has traditionally been adopted, consisting of limited resection (with or without the formation of a defunctioning stoma) followed by palliative chemotherapy.

In recent years, there has been emerging evidence that cytoreductive surgery followed by intraperitoneal chemotherapy may improve survival. However, cytoreductive surgery and intraperitoneal chemotherapy can be associated with considerable perioperative mortality and morbidity, and are highly specialised procedures that are currently only available at selected centres with the requisite expertise.
Systematic review evidence

For patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer, does peritonectomy, with or without perioperative intraperitoneal chemotherapy (PIC), achieve better outcomes in terms of length and quality of life than usual care? (COLMNG3)

A systematic review was undertaken to determine the role of cytoreductive surgery, with or without perioperative intraperitoneal chemotherapy, by comparing it with usual care (limited resection or no resection with or without stoma and/or palliative chemotherapy) in patients with synchronous or metachronous peritoneal metastases from primary colorectal cancer.

The systematic review identified four studies comparing the combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy with usual care. All patients had histologically proven peritoneal carcinomatosis from a primary colorectal cancer. All studies included both patients with primary peritoneal carcinomatosis and patients with metachronous peritoneal carcinomatosis. Two of the four studies also included patients with adenocarcinoma of the appendix, for which the role of cytoreductive surgery and perioperative intraperitoneal chemotherapy is well established. However, appendiceal cancers comprised only 15% and 17.5% of these study cohorts and inclusion of these studies did not alter the outcomes of the systematic review.

All studies were at high risk of bias. All studies were also heterogeneous with a variable number of patients with synchronous and metachronous peritoneal metastases. Different disease staging systems were used across the studies, which made comparisons of outcomes across studies more difficult. Intraperitoneal chemotherapy regimens vary considerably in their timing and the chemotherapy agents used. Variations in regimens both within and between studies further complicated comparisons of outcomes between studies. Median follow up ranged from 17 months to 94 months.

Two randomised controlled trials (RCTs) were identified:

- The Swedish peritoneal study (n = 48) compared cytoreduction plus sequential postoperative intraperitoneal chemotherapy (n = 24) with systemic chemotherapy (n = 24). In the cytoreduction group, 21 patients also received intraperitoneal chemotherapy, while the other three patients only underwent cytoreductive surgery. Complete cytoreduction was achieved in 14 (58%) of patients. Five patients (21%) had no residual nodules greater than 2.5 mm (completeness of cytoreduction [CCR] score of 1), two patients (8%) had residual disease with nodules less than 25 mm (CCR2), and three patients (13%) had residual disease with nodules greater than 25 mm (CCR3). Patients in the chemotherapy arm received 5-FU, leucovorin and oxaliplatin. Although the authors had planned for a sample size of 100, the study was terminated prematurely after 7 years because of slow accrual.

- A Dutch RCT (n = 105) compared the combination of cytoreduction surgery, HIPEC and postoperative adjuvant chemotherapy (n = 54) with systemic chemotherapy using 5-FU and leucovorin (n = 51). Of the cytoreduction group, 41% achieved complete cytoreduction but 41% and 18% respectively had what the authors described as R2-a and R2-b resection (macroscopic residual disease).
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Two cohort studies were identified:

- A multicentre retrospective cohort study[^3] (n = 294) compared cytoreductive surgery plus perioperative intraperitoneal chemotherapy with limited resection (with or without palliative chemotherapy). The sample included 18 patients (6.1%) with stage I disease, 111 (37.8%) with stage II disease, 46 (15.6%) with stage III disease, and 119 (40.5%) with stage IV disease, graded according to peritoneal surface disease severity score. Complete cytoreduction was achieved in 65% of patients, while 25% of patients had CCR1 and 10% had CCR2 or CCR3. Of the 110 patients in the cytoreduction group, 55 (45%) received HIPEC, 19 (17%) received early postoperative intraperitoneal chemotherapy, and 36 (33%) received both HIPEC and early post-operative chemotherapy (5-fluorouracil 650–800 mg/m²).

- A retrospective cohort study[^1] (n = 151) compared patients who underwent cytoreductive surgery (with or without intraperitoneal chemotherapy) with patients who underwent only an ‘open-and-close’ procedure. The sample included 49 patients (32.7%) with a peritoneal carcinomatosis index score (PCI) of 1–10, 45 (30%) with a PCI of 11–20 and 56 (37.3%) with a PCI of 21–39. Of the 128 patients in the cytoreduction group, 57 (44.5%) received sequential postoperative intraperitoneal chemotherapy, 69 (53.9%) received HIPEC and two patients (1.5%) underwent cytoreductive surgery alone. Complete cytoreduction was achieved in 97 (64.7%) of patients. Chemotherapy regimens used for the HIPEC included mitomycin C (n = 2), oxaliplatin in combination with 5-FU and folinic acid (n = 44) and the combination of oxaliplatin, irinotecan, 5-FU and folinic acid (n = 23). Forty-seven patients (37.3%) received neoadjuvant chemotherapy and 27 (21.4%) also received adjuvant systemic chemotherapy.

Perioperative mortality, morbidity and adverse events

Three studies reported treatment-related mortality.[^1][^2][^4] One retrospective cohort study[^1] reported five deaths among 126 patients (8%) in the cytoreduction group within 90 days of treatment. The Dutch RCT[^4] reported seven deaths among 105 patients (6.7%) in the cytoreduction group.[^4] The Swedish peritoneal study reported no 30-day surgical mortality or treatment-related mortality from grade III or IV toxicity.[^2]

High rates of treatment-related morbidity were reported. One retrospective cohort study reported an overall 90-day grade III or IV morbidity rate of 71%.[^1] In a subsequent RCT, 30-day morbidity rate was 33% in patients who underwent cytoreduction.[^2] The same RCT also reported that 6-month treatment-related grade III or IV morbidity was comparable between patients undergoing cytoreduction and intraperitoneal cavity chemotherapy and patients receiving systemic adjuvant therapy (42% versus 50%, p value not reported).[^2] In addition to these complications, seven (29%) of the surgical patients also required an unplanned re-operation for major intra-abdominal complications.[^2]

The other RCT[^4] only briefly reported early surgical and postoperative complications because this was a follow-up study that focused on longer-term outcomes. The investigators reported a mortality rate of 8% (four patients in each of the cytoreduction surgery and intraperitoneal chemotherapy groups). Morbidity rates were not reported quantitatively but the authors stated that treatment related toxicities were high. The initial 2003 publication of this study reported that the most significant complications were small bowel leakage (15%) and post-operative intraabdominal sepsis.[^5] Grade III and IV bone marrow toxicity as a result of mitomycin C within intraperitoneal chemotherapy was noted in 14% and 5% of patients, respectively.
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Treatment termination because of disease progression was also reported in the two RCTs. In both studies, this was less likely in the cytoreduction and intraperitoneal chemotherapy group (21% versus 50% in the Swedish peritoneal study, and 25% versus 86% in the Dutch study).

Survival outcomes

In all four studies, the patients who received cytoreduction with or without intra-peritoneal chemotherapy group showed improved survival, compared with the palliative group. Of the four studies, one reported overall median survival, one reported overall survival, median survival and disease free survival, one reported overall survival, and one reported disease-specific survival.

In the Swedish peritoneal study, 5-year overall survival was significantly higher for patients who underwent cytoreduction and intraperitoneal cavity chemotherapy, compared with those who only received systemic adjuvant therapy (33% versus 4%; p = 0.02). The Dutch RCT reported disease-specific survival of 22.2 months for patients who underwent cytoreduction, compared with 12.6 months for patients who received systemic chemotherapy (p = 0.028). Among patients who had complete cytoreduction (n = 21), median survival was 48 months and 5-year overall survival was 45%.

In the multicentre retrospective cohort study the overall median survival for the palliative surgery group was 9 months, compared with 36 months for cytoreduction and HIPEC, 38 months for cytoreduction and early postoperative intraperitoneal chemotherapy, and 43 months for the combination of cytoreduction, HIPEC and early postoperative intraperitoneal chemotherapy after 17 months median follow up (p < 0.001). The other retrospective cohort study reported that overall median survival was 6.5 months for patients who underwent an ‘open-and-close’ procedure only, compared with 25-34 months for those who underwent cytoreduction and intraperitoneal chemotherapy. This study also reported overall survival rates of 40% for the cytoreduction and HIPEC group, 18% for the cytoreduction and sequential postoperative intraperitoneal chemotherapy group and 0% for the ‘open-and-close’ group after 49 months median follow up (p < 0.001). The same study also reported a 5-year disease-free survival rate of 32% for patients who underwent cytoreduction and HIPEC.

Overall, there is some limited evidence that cytoreductive surgery and intraperitoneal chemotherapy improves survival, but this must be balanced against perioperative mortality and morbidity.

Quality-of-life outcomes

Quality-of-life outcomes were not reported in any of the studies included in the systematic review. There is no evidence to determine differences in quality of life outcomes.

Evidence summary and recommendations

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Evidence summary

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Evidence-based recommendation

For patients with colorectal peritoneal metastases (either synchronous or       | D     |
| metachronous to the primary), consider cytoreduction with perioperative        |
| intraperitoneal chemotherapy. Where this procedure is suitable, offer         |
| referral to a centre with the necessary expertise and infrastructure to        |
| perform this procedure.                                                       |

Evidence-based recommendation

Cytoreduction surgery and perioperative intraperitoneal chemotherapy should    | D     |
| only be offered after due consideration of, and discussion with the patient  |
| about, the potential treatment-related mortality and morbidity.              |

Practice point

Patients with peritoneal carcinomatosis should be referred to a centre with    |           |
| expertise in the management of peritoneal surface malignancies and should be  |
| offered enrolment in a prospective trial, so as to allow further evaluation  |
| of cytoreduction and intraperitoneal chemotherapy.                            |

Practice point

Prior to referral, treating clinicians should have an in-depth discussion with  |           |
| every patient about the potential survival advantage and potential            |
| treatment-related mortality or morbidity.                                     |
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Practice point

All patients’ cases should be discussed at a multidisciplinary team meeting with clinicians who have expertise in the management of peritoneal metastases, to review the relevant clinical information, previous histology (if applicable) and relevant imaging prior to offering patients cytoreductive surgery and intraperitoneal chemotherapy.

Practice point

All patients offered this procedure in established cytoreduction centres should be asked to give their consent for their patient records to be available for ongoing auditing of clinical outcomes. Patients should also be invited and encouraged to participate in research to enable collection of prospective longitudinal data for clinical and quality-of-life outcomes.

Considerations in making these recommendations

Although available evidence is encouraging, there is currently insufficient evidence to recommend the widespread adoption of cytoreduction surgery and intraperitoneal chemotherapy for patients with colorectal peritoneal metastases. Further studies, with appropriate patient selection and outcomes, are needed before cytoreduction and intraperitoneal chemotherapy can be recommended.

Health system implications

Clinical practice

Cytoreduction surgery with perioperative intraperitoneal chemotherapy is a highly specialised treatment that is currently only offered at highly selected centres with the requisite expertise. The management of patients with peritoneal metastases requires a multidisciplinary team approach where the expertise is not restricted to surgical and medical oncology expertise alone.

With increasing evidence for the potential survival benefit of cytoreduction surgery and perioperative intraperitoneal chemotherapy, referrals to centres with the necessary expertise may increase.

Resourcing

The present recommendations would have only a minor effect on resourcing, because they would affect only referral centres with the necessary expertise and infrastructure to perform this procedure.
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It is possible that there may be increased demand for cytoreduction surgery and perioperative intraperitoneal chemotherapy in the future, which may necessitate the development and establishment of more expert centres. The development and establishment of more expert centres should be undertaken in a consultative manner, taking into consideration the expertise and infrastructure available as well as commitment to ongoing audit and research. However, it is still envisaged that these expert centres are likely to be located in large tertiary referral centres, which would require patients from rural and regional areas of Australia to travel large distances for treatment.

**Barriers to implementation**

No barriers to the implementation of these recommendations are envisaged.

**Discussion**

**Unresolved issues**

Prognosis for patients with peritoneal carcinomatosis is poor. There is some suggestion that an elective relook may allow early diagnosis of peritoneal carcinomatosis, resulting in earlier treatment, and therefore lead to improved survival. However, it is unclear whether this is simply the result of lead time bias or whether this represents more effective treatment early in the diagnosis of peritoneal carcinomatosis. Data from long-term prospective RCTs are not currently available.

Cytoreduction surgery, with or without intraperitoneal chemotherapy, requires further prospective evaluation. At present, it is not clear if intraperitoneal chemotherapy is a necessary part of treatment in addition to cytoreduction. Furthermore, even if intraperitoneal chemotherapy is a necessary component of treatment, there is insufficient evidence to conclude which intraperitoneal chemotherapy regimen is most effective in terms of timing and mode of delivery as well as the chemotherapy agent used.

Quality-of-life outcomes have not been included in studies reporting outcomes in patients undergoing cytoreduction with or without intraperitoneal chemotherapy. These need to be evaluated as part of a prospective study.

**Studies currently underway**

No large multicentre randomised trials are currently underway comparing cytoreduction and perioperative intraperitoneal chemotherapy with standard care. However, results are awaited from a RCT recently completed in France, which evaluated the role of HIPEC after cytoreduction surgery.  

Further large RCTs investigating the role of cytoreduction surgery and perioperative intraperitoneal chemotherapy are unlikely. This is partly because variations in practice between expert centres prevent investigators easily reaching consensus on the protocol for a multicentre trial.

Several randomised trials are currently ongoing evaluating the merit of elective relook in patients at high risk of developing peritoneal disease. These may inform the benefit of early treatment of peritoneal metastases.
Future research priorities

The role of cytoreduction surgery and intra-peritoneal chemotherapy requires further evaluation. Future prospective trials should be sufficiently powered to assess the trade-off between increased survival with cytoreductive surgery and perioperative intraperitoneal chemotherapy and the treatment related mortality and morbidity.

These studies should include quality-of-life outcomes and cost-effectiveness outcomes. Reporting of outcomes should be standardised to enable results to be compared between studies.

References


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Appendices

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View pending evidence

View body of evidence

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View literature search

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Systematic review report COLMNG3