Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?

A systematic review of morbidity and mortality

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CRD summary
This review assessed morbidity and mortality of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis and concluded that similar outcomes to other major gastrointestinal surgery may result from careful patient selection. Given poor reporting of the review process, uncertain study quality and paucity of experimental studies, the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis.

Searching
MEDLINE via PubMed was searched for English-language studies from 1966 to August 2008; search terms were reported. Reference lists of relevant articles were manually searched to identify additional articles. Experts were contacted to identify additional unpublished studies.

Study selection
Eligible studies comprised randomised controlled trials, non-randomised controlled trials or well-designed cohort studies and observational studies that assessed morbidity and mortality outcomes of the combined treatment modality of cytoreductive surgery and HIPEC. Where morbidity and mortality outcomes were not comprehensively reported, total number of participants in survival outcome studies had to be greater than 15. Cytoreductive surgery comprised peritonectomy procedures and abdominal colectomy; peritonectomy procedures were not uniformly performed across included studies. HIPEC was administered intraoperatively after the cytoreduction. In some institutions cytoreductive surgery and HIPEC were followed with early postoperative intraperitoneal chemotherapy. Pathological examination was used to confirm peritoneal carcinomatosis from various primary origins. Studies that reported peritoneal dissemination from sarcomas were excluded, unless patients with sarcomatosis were reported within the full morbidity and mortality analysis from the institution. Some institutions were regarded as tertiary high volume institutions (surgeons with high levels of experience). In included studies HIPEC duration ranged from 30 to 120 minutes at a temperature between 39°C and 48°C. Mean duration of the combined procedure, where reported, was 4.9 to 10.5 hours. Where reported, HIPEC regimens included between one and four different drugs at varying doses. Mean number of procedures on each patient varied: 1.2 to 6.4 peritonectomies; 0.6 to 1.2 anastomoses; and 0.9 to 3.0 resections.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted rates of various morbidity outcomes and mortality to calculate percentages; discrepancies were resolved by consensus.

Methods of synthesis
The studies were combined in a narrative synthesis, supported by accompanying data tables. Outcomes were reported separately for tertiary high volume institutions.

Results of the review
Twenty four studies were included in the review (n=2,787, range 18 to 460): four non-randomised controlled trials or
well-designed cohort studies; and 20 were observational studies. Eleven studies were undertaken at high-volume institutions (n=103 to 460).

Mean major or grade III/IV morbidity was 28.8% (range 0% to 52%; six studies); in high-volume centres these ranged from 12% to 52% (nine studies).

Re-operation rates following treatment that occurred in the perioperative period ranged from 0% to 23% (15 studies), sepsis ranged from 0% to 14% (16 studies), fistula from 0% to 23% (20 studies), abscess 0% to 37% (20 studies), haematological toxicity from 0% to 28% (17 studies), ileus from 0% to 86% (18 studies), renal insufficiency from 0% to 7% (18 studies), perforation from 0% to 10% (19 studies), deep vein thrombosis/pulmonary embolus 0% to 9% (17 studies), and anastomotic leak from 0% to 9% (18 studies).

Overall, mean mortality rate was 2.9% (range 0% to 17%, 24 studies); in high-volume centres these ranged from 0.9% to 5.8% (11 studies).

**Authors' conclusions**

Morbidity and mortality outcomes of cytoreductive surgery and HIPEC were similar to major gastrointestinal surgery. To derive maximal benefit of this treatment, careful patient selection with an optimal level of postoperative care must be advocated to avoid undesirable complications of this treatment.

**CRD commentary**

The review question and inclusion criteria were clear. The limited literature search was restricted to publications in English and so publication and language bias may have been present; there were some attempts to locate unpublished material. Methods used for study selection were not reported; therefore, it was unclear whether methods were used to minimise risks of reviewer error and bias. There was no formal assessment of quality of the included studies, which made it difficult to assess the reliability of the included data. Over half of the included studies were small and contained less than 60 patients. Given apparent heterogeneity across studies, a narrative synthesis appeared appropriate. In light of poor reporting of the review process, uncertain study quality and paucity of experimental studies, the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that risks of perioperative morbidity and mortality should be weighted against benefits of survival; cytoreductive surgery and HIPEC were treatment options for suitable patients in whom a curative and life-prolonging treatment was a pursuit.

**Research:** The authors did not state any implications for practice.

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