Hyperthermic intraoperative peritoneal chemotherapy and cytoreductive surgery for people with peritoneal metastases: a systematic review and cost-effectiveness analysis

Kurinchi Gurusamy,[1*] Jeffrey Leung,[1] Claire Vale,[1] Danielle Roberts,[1] Audrey Linden,[1] Xiao Wei Tan,[1] Priyal Taribagil,[1] Sonam Patel,[1] Elena Pizzo,[1] Brian Davidson,[1] Tim Mould,[2] Mark Saunders,[3] Omer Aziz[3,4] and Sarah O'Dwyer[3,4]

[1]Division of Surgery and Interventional Science, University College London, London, UK
[2]Department of Gynaecological Oncology, University College London NHS Foundation Trust, London, UK
[3]Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK
[4]Institute of Cancer Sciences, University of Manchester, Manchester, UK

[*]Corresponding author k.gurusamy@ucl.ac.uk

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Scientific summary

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Background

There is uncertainty about whether hyperthermic intraoperative peritoneal chemotherapy (HIPEC) with cytoreductive surgery (CRS) improves survival and/or quality of life (QoL) compared to CRS or no treatment in addition to systemic chemotherapy in people with peritoneal metastases who can withstand major surgery.

Objectives

Primary objectives

To compare the relative benefits and harms of HIPEC + CRS ± systemic chemotherapy versus CRS ± systemic chemotherapy or systemic chemotherapy alone in people with peritoneal metastases from colorectal, gastric or stage III or greater epithelial ovarian cancers eligible to undergo HIPEC + CRS by a systematic review and meta-analysis.

Secondary objectives

To compare the cost-effectiveness of HIPEC + CRS ± systemic chemotherapy versus CRS ± systemic chemotherapy or systemic chemotherapy alone from the NHS and personal social services (PSS) perspective using a model-based cost–utility analysis.

Methods

We performed a systematic review of literature by searching MEDLINE, EMBASE, Cochrane Library, Science Citation Index, Conference Proceedings Citation Index, as well as trial registers until 14 April 2022. We followed the standard guidance for performing a high-quality systematic review and meta-analysis. We included only randomised controlled trials (RCTs) and assessed the risk of bias using Risk of Bias version 2.0 (ROB 2.0). We were unable to perform an individual participant data (IPD) meta-analysis as planned because of unforeseen circumstances related to coronavirus disease 2019 (COVID-19). This led to trialists who were also clinical researchers being unable to engage for transfer of IPD. We did not foresee that study authors (surgeons) would be sufficiently engaged with providing IPD soon because of the backlog with surgeries and the fatigue induced by COVID-19. Therefore, we performed a meta-analysis based on aggregate data. We calculated the hazard ratio (HR), risk ratio (RR), rate ratio or mean difference (MD) with 95% confidence intervals (CIs) as appropriate. When applicable, we performed meta-analysis using the random-effects model using Review Manager 5.4. We used GRADE guidance to assess the certainty of evidence and determine the strength of recommendations.

For the cost-effectiveness analysis, we performed a model-based cost–utility analysis using methods recommended by The National Institute for Health and Care Excellence (NICE). We estimated the costs and quality-adjusted life-years (QALYs) per patient using lifetime horizon. We calculated the incremental net monetary benefit (incremental NMB) for each comparison based on deterministic analysis and probabilistic sensitivity analysis (PSA). We also performed univariate sensitivity analysis and value of information analysis.

Results

The systematic review included a total of eight RCTs. A total of 955 participants in seven RCTs were included in the quantitative analysis. All comparisons other than those of ovarian cancer contained only one trial.

For colorectal cancer, HIPEC + CRS + systemic chemotherapy probably results in little to no difference in all-cause mortality (60.6% in HIPEC + CRS + systemic chemotherapy vs. 60.6% in CRS + systemic chemotherapy; median follow-up 64 months; HR 1.00, 95% CI 0.63 to 1.58; one trial; 265 participants; moderate-certainty evidence) and may increase the number of people who developed serious adverse events compared to CRS +/– systemic chemotherapy (25.6% in HIPEC + CRS + systemic chemotherapy vs. 15.2% in CRS + systemic chemotherapy; RR 1.69, 95% CI 1.03 to 2.77; one trial; 265 participants; low-certainty evidence). HIPEC + CRS + systemic chemotherapy probably decreases all-cause mortality compared to fluorouracil-based systemic chemotherapy alone (40.8% in HIPEC + CRS + systemic chemotherapy vs. 60.8% in systemic chemotherapy alone; median follow-up 22 months; HR 0.55, 95% CI 0.32 to 0.95; one trial; 105 participants; moderate-certainty evidence).

For gastric cancer, there is high uncertainty about the effect of HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy on all-cause mortality (effect estimates not presented because of very low-certainty evidence). HIPEC + CRS + systemic chemotherapy probably decreases all-cause mortality compared to systemic chemotherapy (40.8% in HIPEC + CRS + systemic chemotherapy vs. 100% in systemic chemotherapy alone; minimum follow-up 24 months; HR 0.40, 95% CI 0.30 to 0.52; one trial; 17 participants; moderate-certainty evidence).

For stage III or greater epithelial ovarian cancer requiring interval CRS, HIPEC + CRS + systemic chemotherapy probably decreases all-cause mortality compared to CRS + systemic chemotherapy (46.3% in HIPEC + CRS + systemic chemotherapy vs. 57.4% in CRS + systemic chemotherapy; median follow-up 32–70 months; HR 0.73, 95% CI 0.57 to 0.93; three trials; 500 participants; moderate-certainty evidence). It may result in little to no difference in health-related quality of life (HRQoL) (MD 4.85, 95% CI −7.74 to 17.44; one trial; 71 participants; moderate-certainty evidence) or number of people who developed serious adverse events compared to CRS + systemic chemotherapy (26.7% in HIPEC + CRS + systemic chemotherapy vs. 25.2% in CRS + systemic chemotherapy; RR 1.06, 95% CI 0.73 to 1.54; two trials; 316 participants; moderate-certainty evidence), although it probably increases the number of serious adverse events per participant compared to CRS + systemic chemotherapy (41.4 events per 100 participants in HIPEC + CRS + systemic chemotherapy vs. 32.6 events per 100 participants in CRS + systemic chemotherapy; rate ratio 1.27, 95% CI 1.09 to 1.49; one trial; 184 participants; moderate-certainty evidence).

The cost-effectiveness analysis included the five comparisons described above: HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy for each of the colorectal, gastric and ovarian cancers and HIPEC + CRS + systemic chemotherapy versus systemic chemotherapy alone for each of the colorectal and gastric cancers.

In people with colorectal peritoneal metastases, the incremental NMBs at willingness to pay (WTP) of £20,000 and £30,000 were −£6162.83 and −£6164.19, respectively, indicating that HIPEC + CRS + systemic chemotherapy was not cost-effective compared to CRS + systemic chemotherapy in NHS. The likelihood of HIPEC + CRS + systemic chemotherapy being cost-effective compared to CRS + systemic chemotherapy was 46.5% and 47.6% at WTP of £20,000 and £30,000, respectively. In the same group of people, the incremental NMBs at WTP of £20,000 and £30,000 were £107,909.46 and £167,621.58, respectively, indicating that HIPEC + CRS + systemic chemotherapy may be cost-effective compared to systemic chemotherapy alone in NHS. The likelihood of HIPEC + CRS + systemic chemotherapy being cost-effective compared to systemic chemotherapy alone was 89.3% and 90.3% at WTP of £20,000 and £30,000, respectively.

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In people with gastric peritoneal metastases, the incremental NMBs at WTP of £20,000 and £30,000 were £14,174.73 and £22,955.89, respectively, for HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy and £81,796.38 and £127,768.23, respectively, for HIPEC + CRS + systemic chemotherapy versus systemic chemotherapy, indicating that HIPEC + CRS + systemic chemotherapy may be cost-effective compared to CRS + systemic chemotherapy or systemic chemotherapy alone in NHS. The likelihood of HIPEC + CRS + systemic chemotherapy being cost-effective ranged between 60% and 70% for the different comparisons and different thresholds.

In women with grade III or greater epithelial ovarian cancer requiring interval CRS, the incremental NMBs at WTP of £20,000 and £30,000 were £46,761.81 and £71,938.23, respectively, indicating that HIPEC + CRS + systemic chemotherapy was cost-effective compared to CRS +systemic chemotherapy in NHS. The likelihood of HIPEC + CRS + systemic chemotherapy being cost-effective compared to CRS + systemic chemotherapy was 71.9% and 72.4% at WTP of £20,000 and £30,000, respectively.

The value of information analysis indicated that the expected value of perfect information (EVPI) ranged between £3 and £53 million for the different cancer types (when estimation was possible) for WTP of £20,000 and £30,000.

Discussion and conclusions

Limitations of the review

We were unable to obtain IPD as planned. IPD would have allowed us to refine our effect estimates for subgroups of people with peritoneal metastases from colorectal, gastric or stage III or greater epithelial ovarian cancer. It is difficult to estimate whether our conclusions would have changed if we had IPD; however, our systematic review and meta-analysis support similar conclusions as the trial authors, suggesting that the impact of IPD may not be major enough to warrant an IPD once the health services have recovered from the impact of COVID-19.

We estimated the HR for survival for gastric cancer trials from Kaplan–Meier curves. This might have introduced bias. However, because of the small number of participants and the estimations that we have performed to calculate the effect estimates, we have concluded that there is uncertainty in the benefit of HIPEC + CRS + systemic chemotherapy in gastric cancers.

Because of the paucity of trials under each comparison, evidence from new RCTs of low risk of bias may change our recommendations. There are concerns regarding the clinical recommendations for people with colorectal peritoneal metastases based on the PRODIGE-7 trial. We have discussed in detail the different concerns raised and why these concerns should not be used as a justification for not basing clinical practice on PRODIGE-7 trial (in the full article). In summary, we based our clinical practice recommendations for colorectal peritoneal metastases on PRODIGE-7 trial because the trial was a low risk of bias trial for the comparison of HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy. An appropriate analysis was used to analyse trial data, and there was no other trial of low of bias comparing HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy. While the CRS + systemic chemotherapy was not directly compared with systemic chemotherapy alone, we recommended CRS + systemic chemotherapy in people with colorectal peritoneal metastases because of the lack of any ‘systemic chemotherapy alone’ treatments that provide equivalent median survival as that observed in the control arm (CRS + systemic chemotherapy) in the PRODIGE-7 trial.

Because of the difficulties in estimating the Peritoneal Cancer Index (PCI) during surgery, we have not recommended HIPEC + CRS + systemic chemotherapy even for the subset of patients with PCI 11–15, but this exploratory subgroup analysis can guide future research.

We have not based our recommendations on non-randomised studies, as we did not find any non-randomised study in which similar participants with colorectal peritoneal metastases underwent HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy or systemic chemotherapy alone. CRS + systemic chemotherapy provides equivalent median survival of 41 months as HIPEC + CRS + systemic chemotherapy. When there is an existing, less invasive treatment that provides equivalent survival, it can hardly be considered life-threatening to warrant recommendations based on low-or very low-certainty evidence.

Recommendations for clinical practice

In people with peritoneal metastases from colorectal cancer, based on the results of PRODIGE-7 trial, HIPEC + CRS + systemic chemotherapy probably results in little to no difference in all-cause mortality or progression-free survival and results in increased complications compared to CRS + systemic chemotherapy. Therefore, HIPEC based on oxaliplatin regimen used in PRODIGE-7 trial + CRS + systemic chemotherapy should not be used in routine clinical practice (*strong recommendation*). Because of the lack of reliability of preoperative or perioperative PCI, the lack of pre-PRODIGE-7 trial standard classification of PCI into PCI < 10, 11–15 and > 15 and pre-defined subgroup analysis based on the PCI classification, HIPEC based on oxaliplatin regimen used in PRODIGE-7 trial + CRS + systemic chemotherapy cannot be recommended for any subgroups.

Because of the median survival observed in the CRS + systemic chemotherapy arm of PRODIGE-7 trial (41 months) and the poor survival observed in people with disseminated colorectal peritoneal metastases (< 12 months in England), CRS + systemic chemotherapy should be offered to people with peritoneal metastases from colorectal cancer when the metastases are confined to the peritoneum and when the patient is likely to withstand major surgery in centres that have experience in performing CRS + systemic chemotherapy (*strong recommendation*).

Because of variability in the results of trials comparing HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy, small number of participants in the trial comparing HIPEC + CRS + systemic chemotherapy versus systemic chemotherapy alone, and the methods used to estimate survival in two trials, there is considerable uncertainty as to whether HIPEC + CRS + systemic chemotherapy or CRS + systemic chemotherapy should be offered to patients with gastric cancer and peritoneal metastases **(no recommendation)**.

Based on three trials showing similar survival benefits in women with stage III or greater epithelial ovarian cancer and metastases confined to the abdomen requiring and likely to withstand interval CRS after chemotherapy, HIPEC + CRS + systemic chemotherapy should be offered routinely to such women in centres with experience in performing HIPEC + CRS + systemic chemotherapy (*strong recommendation*).

The limited number of RCTs for each comparison and paucity of data on HRQoL means that the recommendations may change as new evidence (from trials with a low risk of bias) emerges.

Recommendations for research

For people with peritoneal metastases from colorectal cancer, further research is needed to find out if HIPEC + CRS + systemic chemotherapy using regimens other than those used in PRODIGE-7 are effective compared to CRS + systemic chemotherapy. Since there is uncertainty in the timing of systemic chemotherapy which is unlikely to be resolved before research confirms the effectiveness of HIPEC + CRS + systemic chemotherapy, trial participants can be stratified by whether they received preoperative chemotherapy at the time of randomisation.

For people with peritoneal metastases from gastric cancer, further research is needed to find out which of the three treatments – HIPEC + CRS + systemic chemotherapy, CRS + systemic chemotherapy or systemic chemotherapy alone is better.

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For people with stage III or greater epithelial ovarian cancer, information on the effectiveness of HIPEC + CRS + systemic chemotherapy versus CRS + systemic chemotherapy in people who are eligible to undergo primary CRS is required, but the ongoing trial OVIHIPEC-2 is likely to provide this answer.

All future trials should assess HRQoL and patient-reported outcome measures to allow informed decision-making. If surrogate outcome measures are used as primary outcomes, the validity of such outcomes as good surrogate outcomes for longevity of life, HRQoL and/or patient-reported outcome measures should be considered while arriving at conclusions.

Study registration

This study is registered as PROSPERO CRD42019130504.

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