



## Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic exploration report number:	TER311
Topic:	Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis.
Summary of findings:	<p>A 2021 National Institute for Health and Care Excellence (NICE) interventional procedures guidance 688 (IPG688) evaluated the efficacy and safety of cytoreduction surgery (CRS) with hyperthermic intraoperative peritoneal chemotherapy (HIPEC). It recommended that CRS with HIPEC should only be used with special arrangements for clinical governance, consent, audit or research.</p> <p>This topic exploration report identified a health technology assessment (HTA) report, four systematic reviews, one primary study and four economic evaluations. To summarise, the studies found in this topic exploration report varied in their comparator and objective. The main outcomes were greater overall survival outcomes, five-year survival and disease-free survival compared with systemic chemotherapy or CRS alone. Two systematic reviews used observational data in their analysis (Flood et al. 2020; Flood et al. 2021), and two systematic reviews used randomised controlled trials in their methodology (Eveno and Pocard 2020; Kitai 2020). Several authors stated the need for a higher number of randomised controlled trials evaluating CRS and HIPEC for the treatment of peritoneal carcinomatosis.</p> <p>A recent health technology assessment reported that older treatment methods (surgery and/or systemic chemotherapy) reported lower overall survival, indirectly suggesting the superiority of the CRS with HIPEC procedure. One economic study showed that CRS with HIPEC for peritoneal carcinomatosis has the potential to be cost-effective.</p>

## Introduction and aims

Peritoneal carcinomatosis is an advanced form of cancer resulting from the regional spread of gastrointestinal, gynaecological and other malignancies. Cytoreduction surgery is done to remove all macroscopic tumours within the abdominal cavity. Hyperthermic intraoperative peritoneal chemotherapy is then used to distribute a chemotherapeutic drug uniformly to all surfaces within the abdominal cavity and to increase drug penetration. This is done to treat any remaining microscopic traces of the cancer.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis compared to standard/current care, which included systemic chemotherapy (alone or with surgery), closed peritoneal instillation of chemotherapy, or surgery alone.

## Evidence overview

### Health technology assessments (HTA)

We identified one HTA entitled 'Cytoreductive surgery and intraperitoneal chemotherapy (HIPEC or EPIC) in patients with colorectal adenocarcinoma and peritoneal carcinomatosis' by Ludwigs et al. 2013 which recommended that there is moderate quality of evidence for prolonged survival (22.4 versus 12.6 months) by CRS with HIPEC versus systemic chemotherapy in patients with colorectal cancer and isolated peritoneal carcinosis. The effects on health-related quality of life were unknown at the time.

### Guidance

The National Institute for Health and Care Excellence (NICE) produced interventional procedures guidance (IPG688), on the safety and efficacy of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. The IPG688 recommendations conclude that the procedure showed frequent and serious, but well-recognised complications, and evidence on the efficacy of the procedure was limited in quality. Thus, it was recommended that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

IPG688 was informed by a rapid review that searched for evidence up to 26 October 2020. The rapid review was based on 19,109 patients from six meta-analyses, three systematic reviews and one randomised controlled trial. However, there was an overlap of primary studies in some systematic reviews and meta-analyses. Primary studies (other than randomised controlled trials not included in the systematic reviews) were excluded from the overview. Thus, the following search for systematic reviews by Health Technology Wales for evidence on the clinical effectiveness will cover from 2020 to present.

### Systematic reviews

Health Technology Wales identified four systematic reviews relating to the clinical effectiveness of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy. The objective, study selection and method varied across each systematic review such as comparing cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy with or without liver resection. Studies also varied in primary cancer site, such as colorectal, ovarian and gastric cancer.

One systematic review included 38 published randomised controlled trials and several ongoing trials for further analysis comparing the CRS and HIPEC with systemic chemotherapy or CRS alone (Eveno

and Pocard 2020) whilst Kitai 2020 used a mixture of randomised controlled trials, retrospective and observational studies using either single arm studies or comparing CRS and HIPEC to standard systemic chemotherapy. Both Flood et al. 2020 and Flood et al. 2021 used comparative cohort studies to compare CRS and HIPEC with systemic chemotherapy or CRS alone.

The main outcomes included overall survival, five-year survival and disease-free survival. All the reviews explicitly reported improved disease-free survival with CRS and HIPEC, however the choice of comparator did vary (Flood et al. 2021, Flood et al. 2020, Kitai 2020, Eveno & Pocard 2020). Kitai et al. (2020) found that CRS and HIPEC resulted in long-term survival with acceptable perioperative morbidity. Eveno and Pocard (2020) reported outcomes about survival rates and postoperative morbidity depending on the organ of origin (colorectal, ovarian and gastric cancer). In their conclusion, they reported that there is some evidence that CRS and HIPEC improves survival in recurrent colorectal origin but the evidence in ovarian and gastric cancer remains debated.

All authors noted the need for further research on the topic area. Several authors stated the need for a higher number of randomised controlled trials evaluating CRS and HIPEC for the treatment of peritoneal carcinomatosis. Eveno and Pocard (2020) concluded that the trial design and interpretation of results remain difficult because of multiple methodological challenges. Flood et al. (2020) reported that more evidence is urgently required to contribute to multidisciplinary and international consensus on treatment strategies.

#### Primary studies

We identified one recent study comparing singular and repeated CRS with HIPEC (Bekhor et al. 2020). It concluded that repeated CRS and HIPEC for peritoneal carcinomatosis had similar perioperative morbidity and mortality, as well as long-term oncological benefits, when compared with singular CRS and HIPEC. However, more than twice as many patients undergoing repetitive CRS and HIPEC suffered from major late complications (Bekhor et al. 2020). This study recommended that the risks and benefits of the procedure should be considered on a case-by-case basis.

#### Economic evidence

Health Technology Wales identified four studies about the cost-effectiveness of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy (Hamilton et al. 2019, McBride et al. 2021, Koole et al. 2019, Lee et al. 2018). Studies varied in the primary cancer of the study population.

When evaluating the cost effectiveness of CRS with HIPEC for peritoneal carcinomatosis compared to systemic chemotherapy, findings show that CRS and HIPEC results in prolonged survival for selected patients and a lower cost per life year.

Hamilton et al. (2019) developed a Markov model to evaluate the cost-effectiveness of CRS with HIPEC compared with systemic chemotherapy for isolated peritoneal carcinomatosis from metastatic colorectal cancer (mCRC) and concluded that the CRS with HIPEC procedure is a cost-effective treatment for isolated peritoneal carcinomatosis from metastatic colorectal cancer in the United States. The incremental cost-effectiveness ratio (ICER) for treatment with CRS/HIPEC compared with systemic chemotherapy was \$91,034 per QALY gained. The likelihood of CRS and HIPEC being a cost-effective strategy at the willingness-to-pay (WTP) threshold was 87%, based off a threshold of \$100,000 per QALY.

#### Ongoing research

There is an ongoing clinical trial based in France which was first registered with Scan Medicine in December 2019 entitled, 'Intensive intraperitoneal therapy in advanced ovarian cancer combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and postoperative intraperitoneal chemotherapy (IPC)'. The completion date is unknown. The success of the

combination of HIPEC and IPC will be evaluated with two co-primary endpoints, the feasibility rate, and the toxicity rate.

### Areas of uncertainty

Most studies in this topic exploration report use observational data. Few studies used randomised controlled trials in their study design.

One systematic review suggested that ongoing studies are underway to further assess the effectiveness and safety of this intervention. However, we only identified one ongoing study, with an unknown completion date.

We identified evidence comparing CRS and HIPEC with systemic chemotherapy or CRS alone. If this topic were to proceed to fuller appraisal, consideration would be needed as to what comparator would be appropriate to include.

## Literature search results

### Health Technology Assessments and Guidance

Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis - NICE Interventional procedures guidance [IPG688] Published: 03 March 2021. Available at: <https://www.nice.org.uk/guidance/ipg688>

Cytoreductive surgery and intraperitoneal chemotherapy (HIPEC or EPIC) in patients with colorectal adenocarcinoma and peritoneal carcinomatosis. Ludwigs et al. 2013. Available at: <https://database.inahta.org/article/13613> Published: 2013

Cytoreductive surgery (peritonectomy) with hyperthermic intraperitoneal chemotherapy (HIPEC). National Committee for Technology Incorporation (Conitec). Available at: <https://database.inahta.org/article/19547> Published: 2020

### Evidence reviews and economic evaluations

Flood M, Das A, Soucisse M, et al. (2021). Synchronous Liver Resection, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Liver and Peritoneal Metastases: A Systematic Review and Meta-analysis. *Diseases of the colon and rectum*. 754-64. doi: 10.1097/DCR.0000000000002027. Available at: <https://pubmed.ncbi.nlm.nih.gov/33742615/>

Flood M, Narasimhan V, Waters P, et al. (2020). Survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: A systematic review and discussion of latest controversies. *The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*. doi: 10.1016/j.surge.2020.08.016. Available at: <https://pubmed.ncbi.nlm.nih.gov/33023847/>

Kitai T. (2020). The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal carcinomatosis: a systematic review including evidence from Japan. *Surgery today*. doi: 10.1007/s00595-020-02180-7. Available at: <https://pubmed.ncbi.nlm.nih.gov/33185798/>

Eveno C, Pocard M. (2020). Randomized controlled trials evaluating cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in prevention and therapy of peritoneal metastasis: a systematic review. *Pleura and peritoneum*. 1: 169-82. doi: 10.1515/pp-2016-0027. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6386515>

Hamilton TD, MacNeill AJ, Lim H, et al. (2019). Cost-Effectiveness Analysis of Cytoreductive Surgery and HIPEC Compared With Systemic Chemotherapy in Isolated Peritoneal Carcinomatosis From Metastatic Colorectal Cancer. *Ann Surg Oncol*. 26(4): 1110-7. doi: 10.1245/s10434-018-07111-y. Available at: <https://pubmed.ncbi.nlm.nih.gov/30690682/>

Koole SN, van Lieshout C, van Driel WJ, et al. (2019). Cost Effectiveness of Interval Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer on the Basis of a Randomized Phase III Trial. *J Clin Oncol*. 37(23): 2041-50. doi: 10.1200/jco.19.00594. Available at: <https://pubmed.ncbi.nlm.nih.gov/31251694/>

Lee ZJ, Chia SL, Tan G, et al. (2018). Cost Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Management of Colorectal Peritoneal Carcinomatosis. *Ann Surg Oncol*. 25(8): 2340-6. doi: 10.1245/s10434-018-6508-4. Available at: <https://pubmed.ncbi.nlm.nih.gov/29948417/>

McBride KE, Steffens D, Solomon MJ, et al. (2021). Cost-analysis of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal malignancy: An Australian perspective with global application. *Eur J Surg Oncol.* 47(4): 828-33. doi: 10.1016/j.ejso.2020.09.010. Available at: <https://pubmed.ncbi.nlm.nih.gov/32972815/>

#### Individual studies

Bekhor E, J C, Hofstedt M, et al. (2020). The Safety of Iterative Cytoreductive Surgery and HIPEC for Peritoneal Carcinomatosis: A High Volume Center Prospectively Maintained Database Analysis. *Annals of surgical oncology.* 27: 1448-55. doi: 10.1245/s10434-019-08141-w. Available at: [https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=31873928](https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=31873928)

#### Ongoing research

‘Intensive intraperitoneal therapy in advanced ovarian cancer combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) and postoperative intraperitoneal chemotherapy (IPC)’. Available at: <https://scanmedicine.com/clinicaltrials/2019-003357-29%2FFR>

<b>Date of search:</b>	<b>31<sup>st</sup> August - 2<sup>nd</sup> September 2021</b>
<b>Concepts used:</b>	“Cytoreduction surgery” and/or “hyperthermic intraoperative peritoneal chemotherapy” and “peritoneal carcinomatosis”