

# Balancing the books for cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal metastases in a diminishing economy: a global issue

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## Abstract

Medical advances, particularly technological and pharmaceutical, are continually increasing, and this pattern is likely to continue. In contrast to this technological and pharmaceutical expansion, the reality of a global recession and the need to *cut costs* are universal health-care challenges.

Herein the authors review the approximate cost estimates for a proven strategy to manage colorectal peritoneal metastases, namely cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy and different tools government or health care providers use in deciding which treatments to fund and remunerate.

## Introduction

Whilst the technological explosion in the last 20 years has been met with great excitement by doctors, scientists and members of the public, the global recession of the early 21<sup>st</sup> century

brings with it a sobering challenge to healthcare providers. In England, at the end of 2014, the CEO of NHS England, Simon Stevens, formulated a *Five-year forward view* to help tackle a large gap between the limited money available and the need for continued funding of essential services - a gap of over £30 billion over 5 years.

Whilst there is a seemingly unending list of investigations and treatment options available to doctors and surgeons, we have a professional obligation to strike the balance of being fiscally responsible (or rather, not unduly profligate) whilst maintaining patient safety. When considering treatments, whether drugs or procedures, the following three questions should be considered: i) *Efficacy* - Can the treatment or intervention work? This will involve proof of effect, often referred to as *Proof of Principle*, usually in carefully selected cases in well controlled environments; ii) *Effectiveness* - Does it work? This involves broader application across different centres and populations; iii) *Cost-Effectiveness* - Is the treatment, or intervention, cost effective?

These guiding principles are the basis for NICE (National Institute for Health and Care Excellence) in the UK. Guidelines on specific drugs, interventions and procedures can be found in the NICE website [www.nice.org.uk](http://www.nice.org.uk) and are a useful, freely available, resource.

In the context of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy (CRS-HIPEC) in a diminishing global economy, the key aspects are undoubtedly focussed on the *Cost-effectiveness*, though of course there are ongoing issues around efficacy, effectiveness, and safety, particularly in emerging centres. It must be stated however that *Cost-effectiveness* for an individual treatment is contentious. Throughout whilst discussing cost effectiveness, the authors are comparing CRS-HIPEC to standard care, which we believe to be poor, which is palliative chemotherapy.

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Key words: Cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; colorectal cancer; peritoneal metastases.

Contributions: JB researched and wrote the first draft; BJM reviewed it and both agreed on the final version.

Conference presentation: paper presented at the 10<sup>th</sup> International Congress on Peritoneal Surface Malignancies, Washington, DC, November 17-19, 2016.

Received for publication: 9 January 2017.  
Revision received: 29 January 2017.  
Accepted for publication: 3 February 2017.

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*Journal of Peritoneum (and other serosal surfaces) 2017; 2:53*  
doi:10.4081/joper.2017.53

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## Background and review of data

As most surgeons are aware, surgical resection cures selected patients with colorectal liver or lung metastases, or local recurrence. In contrast, until recently peritoneal spread has been considered inevitably fatal. However accumulating evidence suggests that selected patients can now be cured by a combination of CRS and HIPEC. The concept of *operable colorectal peritoneal metastases* (CPM), as opposed to *peritoneal carcinomatosis*, demands clear definition in order to identify this subset of patients with treatable, and curable disease.<sup>1</sup>

Few surgeons question the benefit of liver surgery for resectable liver metastases, yet there is no randomised controlled

trial showing benefit. This is in contrast to the situation in selected patients with colorectal peritoneal metastases where Verwaal and colleagues reported an improvement in median survival from 12 to 22 months in a randomized controlled trial in 2003.<sup>2</sup>

CRS was initially utilised in the treatment of pseudomyxoma peritonei (PMP) characterized by mucinous ascites predominantly from a ruptured tumour of the appendix. While PMP was traditionally considered benign, progression of mucinous ascites eventually results in gastrointestinal tract compression, bowel obstruction and cardiorespiratory compromise, eventually culminating in death unless adequately treated. Thus at its best, PMP should be considered a borderline malignancy (Moran and Cecil). Although, the biology of PMP and colorectal peritoneal metastases differs, the treatment strategy of CRS and HIPEC, which has generally evolved from the treatment of PMP, is also applicable to other peritoneal tumours such as primary peritoneal mesothelioma and colorectal peritoneal metastases.<sup>2,3</sup> Evidence is accumulating that CRS-HIPEC can offer a survival advantage to selected patients with colorectal peritoneal metastases in an RCT, case series<sup>2,4</sup> and NICE guidelines (see below).

Thus while there is little doubt about the effectiveness of CRS-HIPEC in appropriate cases (a complete cytoreduction is necessary to provide a survival benefit) as compared to standard chemotherapy - there still remains the issue of funding this expensive, and high risk, treatment strategy in a diminishing economy.

Fortunately there is some good independent evidence available on the NICE evaluation for both PMP (<https://www.nice.org.uk/guidance/ipg56>) and for what was termed colorectal carcinomatosis (or what we now call colorectal peritoneal metastases; <https://www.nice.org.uk/guidance/ipg331>).

Both evaluations warn about complications and safety and recommend specialization and centralization as crucial.

There are 4 main tools that health economists use for formal economic evaluation.<sup>2</sup> These are cost minimisation analysis; cost effectiveness analysis, cost utility analysis and cost benefit analysis.

#### Cost minimisation analysis

This is purely a comparison of the cheapest option on offer and generally there is little or no emphasis on which is *better for the patient*. In the case of colorectal peritoneal metastases, 6 cycles of palliative chemotherapy is cheaper than CRS-HIPEC and hence might be recommended in a cost minimization analysis.<sup>5</sup>

#### Cost effectiveness analysis

This is a common tool used to compare interventions, which have a common outcome measure *e.g.* median survival. Data is presented in a ratio and an agreed figure is applied for comparative purposes *e.g.* £40,000 per life year saved.<sup>5</sup> It is clear from the RCT by Verwaal<sup>2</sup> that there is an improved outcome with CRS-HIPEC as compared to standard medical treatment.

#### Cost utility analysis

This seeks to include not only quantitative data such as life years saved, but also qualitative data and aims to balance cost against effectiveness. The commonest cost utility analysis healthcare providers may be aware of is the *Quality adjusted life year* (QALY).<sup>5</sup> There is good evidence outline below that patients undergoing CRS-HIPEC have a good quality of life.

#### Cost benefit analysis

This takes into account all of the costs and consequences in monetary terms.

It is now accepted that CRS-HIPEC does offer a clear survival advantage in selected patients, but at a high cost. Healthcare serv-

ices may look for efficiency, almost certainly from high-volume centres and central healthcare specialised funding is likely to provide the best cost-benefit outcome.<sup>5</sup>

## Discussion

In terms of material costs, there is some anecdotal and published evidence that hospitals are not being remunerated equally for the cost of these procedures. One French study,<sup>6</sup> albeit 11 years old now, reported that the mean cost per patient undergoing CRS-HIPEC for the hospital was approximately 40,000 Euros. The mean financial income per patient, per case, was just over 20,000 Euros. This approximate cost and similar financial deficit has also been reported by researchers in Italy<sup>7</sup> and to a lesser extent in Germany.<sup>8</sup> Many European countries use a *Diagnosis-related group system* (DRG) and there is concern that this may be a causative factor in inadequate remuneration.

Most of the financial burden of these cases is comprised of intensive care cost, followed by the hospital ward stay and operating theatre costs.<sup>9</sup> A comparison of the variations in costs is outlined in Table 1. It is interesting to compare these with the data published by Brian Seal, from the USA, on the comparison of treatment costs of colorectal cancer (chemotherapy/biologics/inpatient/outpatient and total cost per patient).<sup>10</sup>

There is evidence that survivors of CRS and HIPEC have excellent post-operative quality of life which is an important factor to consider in making financial considerations as outlined above.<sup>11</sup> One of the largest series in the world had shown that health-related quality of life was affected early post-operatively a one would expect, but values returned to near baseline between 6 to 12 months post-operatively. This trend improved through the 3<sup>rd</sup> year post-operatively. Adjuvant interventions, such as emotional and psycho-social support, are clearly beneficial and contribute to the holistic and multi-modality approach of care. This data has been corroborated by other studies.<sup>12,13</sup>

An important concept by Vanounou and Garfinkle, quantifying *patient value* as the sum of survival benefit and quality of life, seems the optimal way of rationalizing costing and cost-effectiveness.<sup>14</sup> They recognise that individually cost and clinical-benefit cannot be viewed in isolation and need not be mutually exclusive. They combine these elements and believe that from a *value based medicine* perspective, CRS-HIPEC is a valuable tool in the surgical oncologist's armamentarium for appropriate cases of peritoneal disease.

## Conclusions

It is clear that cost and cost effectiveness of CRS and HIPEC for colorectal peritoneal metastases is an immensely complicated topic with high risks for patients, surgeons and healthcare systems.

**Table 1. Comparison of the variations in costs.**

Country	Mean cost/procedure (Euros)
Australia	36,173
Germany	20,213
France	39,358
Italy	36,015

We have a duty to our patients and our healthcare system funders to set up and deliver treatment centres carefully and seek help and support from established units to select suitable cases for this rewarding but complex strategy of CRS and HIPEC.

Work must continue, through PSOGI and other channels to explore the principles of efficacy, effectiveness and cost-effectiveness.

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