Hyperthermic Intraperitoneal Chemoperfusion (HIPEC) and Cytoreductive Surgery (CRS) for Peritoneal Malignancy (PM) from Colorectal and Appendiceal Primary Cancers

Review information

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Dates

<table>
<thead>
<tr>
<th>Assessed as Up-to-date:</th>
<th>20 October 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Search:</td>
<td>12 September 2014</td>
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<td>Next Stage Expected:</td>
<td>31 October 2014</td>
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</table>
Abbreviations and definitions

General

CCS – Completeness of Cytoreduction Score
CE – Cost Effectiveness
CEEG – Clinical Effectiveness and Evaluation Group
CI – Confidence Interval
CT – Computed Tomography
CHPP – Continuous Health Peritoneal Perfusion
CRS – Cytoreductive Surgery
CRC – Colorectal Cancer
CRPC – Colorectal Peritoneal Carcinomatosis
DFS – Disease free survival
EASR – European Age Standardised Rate
EPIC – Early Postoperative Intraperitoneal Chemotherapy
HIPEC – Hyperthermic Intraperitoneal Chemoperfusion
MMC – Metomyocin C
MRI – Magnetic Resonance Imaging
OR – Odds Ratio
OS – Overall survival
PC – Peritoneal Carcinomatosis
PCI – Peritoneal Cancer Index
PET – Positron Electron Tomography
PM – Peritoneal Malignancy
PMP – Pseudomyxoma peritonei
PSS – Prior Surgical Score
QOL – Quality of Life
SC – Standard care (in this document this refers to systemic chemotherapy plus or minus palliative surgery)
SPCI – Simplified Peritoneal Cancer Index
Quality of life instruments

The Medical Outcomes Study Health Survey, Short Form (SF-36)

The SF-36 is a 36-item generic health measure that assesses eight areas of perceived health: physical functioning (PF), role-physical (RP), role-emotional (RE), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), and mental health (MH). For PF, the patient is asked to rate the degree to which ten activities (vigorous activity, moderate activity, lifting and carrying groceries, walking several flights of stairs, walking one flight of stairs, and kneeling or stooping, walking greater than a mile, walking several blocks, walking one block, bathing and dressing) are limited on a scale with three possible descriptors (not limited, limited a little and limited a lot). A higher score indicates better functioning. Standardised scores range from 0 to 100 and have been reported on a variety of different patient populations.

The Brief Pain Inventory—Short Form (BPI)

The BPI is a 14-item, self-report instrument designed to assess pain in cancer patients and persons with other diseases. The BPI measures both the intensity of pain (sensory dimension, six items plus one item regarding current medications) and interference of pain in the patient’s life (reactive dimension, seven items). Since pain may be a likely outcome of aggressive treatment and/or disease progression, it is a particularly important area to measure in this patient population.

The Centre for Epidemiologic Studies–Depression Scale (CES-D)

The CES-D is a 20-item self-report measure developed to screen for depressive disorders. It has high sensitivity and positive predictive value for detecting depressive disorders (major depression and dysthymia). Cut-off scores indicate the likelihood that a subject meets DSM-IV criteria for the diagnosis of depression. A score of >16 or 17 has been used as the cut-off score with higher scores indicating significant depressive symptoms.

The Eastern Cooperative Oncology Group (ECOG) Performance Status Rating Scale

This is a single item rating of activity level where 0 = fully ambulatory without symptoms; 1 = fully ambulatory with symptoms; 2 = requiring bed rest (or equivalent)
less than 50% of the waking day; 3 = requiring bed rest (or equivalent) greater than
50% of the waking day; and 4 = bedridden.

**The Functional Assessment of Cancer Therapy—Colon Scale (FACT-C)**

The general version of the Functional Assessment of Cancer Therapy (FACT-G) is a
27-item self-report questionnaire that measures QOL in cancer patients. The FACT-
C is the FACT-G plus the 9-item colon subscale. We chose the colon subscale
because it includes items that best address symptoms associated with peritoneal
carcinometasis (PC) and there is currently no FACT subscale specifically designed
for PC patients. The FACT consists of four subscales measuring physical (PWB),
functional (FWB), social/family (SFWB), emotional well-being (EWB). A trial outcome
index (TOI) representing PWB + FWB + the C subscale was used as a measure of
treatment impact on physical symptoms and functioning. The FACT can be either
self-administered or used in an interview format and is easily completed in 5-10 min.
Patients are asked to rate themselves on how they feel today and over the past 7
days on a Likert scale from 0 (not at all) to 4 (very much). The FACT-G provides
subscale scores and a total QOL score. A higher score indicates better QOL.
Cronbach’s Alpha for each subscale has been reported as follows: PWB (0.82); FWB
(0.80); SFWB (0.69); EWB (0.74); and total FACT-G (0.89).

**Pittsburgh Sleep Quality Index (PSQI)**

The Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality and disturbances
over the past 4 weeks. Nineteen of the 24 items are client-rated and used in score
tabulation. The scorer assigns an ordinal score, ultimately deriving a global score
and seven component scores (sleep quality, sleep latency, sleep duration, habitual
sleep efficiency, sleep disturbance, use of sleeping medication, and daytime
dysfunction). Component scores (i.e., 0–3) are given equal weight, indicating a
possible global score of 0–21. Lower scores reflect better sleep quality. A component
score of “0” indicates no difficulty; “3” reflects severe difficulties. A global cut-off
score of 5 was established to denote clinically significant sleep impairment. A score
above this cut-off suggests severe problems in a minimum of two areas or moderate-
intensity problems in three or more. Scores, therefore, inherently reflect both the
number and severity of sleep–wake disturbances.

**Definitions**

*Peritoneal cavity* – the space between the two membranes that separate the
organs from the abdomen
Peritoneal carcinomatosis – traditionally regarded as an ‘end stage’ progression of abdominal cancers arising from a number of different primary seeds (e.g. appendiceal, colorectal, ovarian, mesothelium, gastric).
Technical Summary

Colorectal Cancer

The overall grade of evidence for the clinical effectiveness of CRS plus HIPEC is moderate to strong. There was a statistically significant and consistent improvement in survival at 2 and 5-years compared to standard of care. The single RCT identified did have methodological flaws in its design. This was due to the break in protocol to allow patients pre-treated with systemic chemotherapy to be included 12 months after the start of the protocol and the choice of the comparator (5-FU chemotherapy plus or minus debulking surgery has evidence of poor effectiveness). This may have overestimated the comparative effect size of the CRS plus HIPEC arm to standard care. However, subsequent comparative case series studies using different chemotherapy regimens support the effect sizes on survival noted in the RCT although these studies suffer from potential bias due to their non-randomised study design.

There was evidence of the prognostic relationship between completeness of cytoreduction, distribution and volume of metastatic spread in the abdomen, presence or absence of co-morbidities, extra-abdominal tumour burden and poor performance status at baseline being predictive of poorer outcome. These criteria are captured in a variety of prognostic tools that have been developed as part of the development of the intervention.

The use of different chemotherapy agents in the HIPEC protocol within the studies evaluated causes uncertainty in the interpretation of the results (e.g. Leucovarin, oxaliplatin, cisplatin, MMC, mephalan) as does the timing of the HIPEC (during, early or late). It is plausible that these different reagents and the timing of the HIPEC may have different impacts on effectiveness and survival.

Reported mortality, morbidity and recurrence rates are high in earlier case series data with evidence for some modest improvements, possibly related to the cytotoxicity of the chemotherapy agents used during HIPEC, in later case series studies.

The QOL data is based on both peri-operative assessment and in long-term survivors using a variety of validated QOL instruments. These instruments have been applied however to a heterogenous population with different primary cancers so the data is difficult to interpret and causes uncertainty in estimating effect sizes. Generally, patients suffer a dis-utility in QOL up to 3 months post procedure with survivors having gradual improvements in QOL over time. Whether patients post CRS and HIPEC achieve comparable QOL to a case matched cohort or a normal population is uncertain. There is evidence that physical if not mental deficit remains
even in survivors. There was evidence linking poor QOL to the same prognostic criteria described for poor survival.

There was only one study reporting on cost effectiveness for a heterogenous mixed population of appendiceal, colorectal, gastric and ovarian primary cancers. The study had a number of methodological flaws including lack of modelling on recurrence rates and an assumption of only 6 months survival on standard care (underestimating the survival benefits of systemic chemotherapy plus or minus palliative surgery in the control arms of the study). These effects probably overestimated the calculated cost effectiveness (based on calculated cost per life year) of the CRS plus HIPEC arm of the study. No sensitivity analysis was conducted. The study adopted a cost: benefit approach which therefore did not take into account the data on QOL available. Better data on cost effectiveness would be needed to confirm the estimations based on this single study.

**Appendiceal Cancer**

There was both lower quantity and quality of evidence for this group. The overall grade of evidence for the clinical effectiveness of CRS plus HIPEC was poor to moderate with a statistically significant and consistent improvement in survival at 2- and 5-years compared to standard of care.

There was evidence for a similar relationship with the completeness of cytoreduction, distribution and volume of metastatic spread in the abdomen, presence or absence of co-morbidities, extra-abdominal tumour burden and poor performance status at baseline being predictive of poorer outcome. These criteria are captured in a variety of prognostic tools that have been developed as part of the development of the intervention.

The QOL evidence identified comprised of the same studies derived for colorectal cancer and the same limitation apply.

The mortality and morbidity evidence was similar to CRS plus HIPEC in the colorectal scenario.

The same study on cost-effectiveness was identified and the same limitations apply as described above.
Plain language summary

Peritoneal malignancy (PM) is an advanced form of cancer found in the peritoneal cavity – the fluid-filled gap between the walls and the organs contain in the abdomen. This type of cancer occurs due to dissemination of primary tumour from the appendix, colon, rectum or ovaries. It is associated with short survival and poor quality of life.

Cytoreductive surgery (CRS) refers to the destruction of visible tumour throughout the abdomen. This is then combined with hyperthermic (warm) intraperitoneal chemotherapy (HIPEC) to increase the effectiveness of the combined treatment.

There is moderate to good quality evidence based on systematic review and meta-analysis for the clinical effectiveness of CRS plus HIPEC in highly-selected patients with PM of colorectal origin.

There is poor to very poor data based on case series data available for the clinical effectiveness of CRS plus HIPEC in highly selected patients with PM of appendiceal origin. The majority of data for this tumour sub-type was available for patients who developed pseudomyxoma peritonei, a different disease which was outside of the scope of this review.

There is moderate to poor quality evidence that quality of life is improved from about three months following the procedure. Quality of life responses were higher in well selected patients.

In long-term follow-up, there was conflicting evidence for survivors whether they have similar QOL to that of a matched group of other cancer survivors, or if significant physical deficit remains in patients who had CRS plus HIPEC.

There is poor to moderate quality evidence for safety for CRS plus HIPEC. The evidence available shows that CRS plus HIPEC carries a significant risk of mortality, morbidity and adverse events.

There is poor quality evidence on recurrence rates following CRS plus HIPEC. The evidence available suggests a high recurrence rate which required 2nd and 3rd repeat interventions in the studies assessed.

The evidence on cost effectiveness is limited to a single study. This shows that in highly selected patients CRS plus HIPEC may be cost effective but that the CI are large. The approach adopted in this study was based on a deterministic approach to cost benefit yielding a cost per life year analysis which did not take into account any data on QOL for this patient group and was based on a cost per life year calculation.
Background
Description of the condition

Epidemiology

Colorectal Cancer
Colorectal cancer (CRC) or ‘bowel cancer’ is a key public health issue in Wales, accounting for 14% of total cancer burden. There were 474 more cases of CRC in 2012 than in 2003, making this the most common cancer in Wales in 2012 (Figure 1). This is the first time this has happened since our records began. The ageing of the population during this time played a part (Figure 2). Increased awareness and the introduction of bowel screening may also be responsible, but the causes are not certain.

Figure 1. Number and proportion of the five most common types of cancer diagnosed in Wales. All persons, all ages. 2012

![Pie chart showing the five most common types of cancer diagnosed in Wales in 2012: Bowel (14%), Lung (13%), Breast (12%), Prostate (13%), Other (63%).]

Source: Welsh Cancer Intelligence and Surveillance Unit’s Cancer Registry
www.wcsi.wales.nhs.uk

Figure 3 shows the commonest causes of cancer deaths in Wales based on data from 2012. Lung cancer accounted for almost 22 per cent of all cancer deaths in 2012 (Figure 3). At 1,894 deaths, it accounts for most cancer deaths, ahead of other common cancers such as CRC, breast and prostate, and more than bowel and breast combined. These cancers also have the highest mortality rates (Figure 4).
Figure 2. Bowel cancer incidence (EASR) in Wales by sex, all ages. 2003-2012

Figure 3. Number of deaths from different cancers, 2012
Appendiceal Cancer

Malignant tumours of the appendix are rare tumours, accounting for 0.2% to 0.5% of all cancers of the gastrointestinal tract and diagnosed in 0.9% to 1.4% of appendectomy specimens. Carcinoid tumours are the most common, comprising over 50 percent of appendiceal neoplasms in most series. However, the distribution of appendiceal neoplasms might be changing over time. In a large series of appendiceal tumours derived from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute between 1973 to 2003, the most frequent histology was a mucinous adenocarcinoma followed by intestinal-type adenocarcinoma; carcinoid tumours comprised only 11%.

Peritoneal Malignancy (PM)

Peritoneal malignancy includes any dissemination of tumour inside the abdomen. This clinical scenario occurs when a cancer arises either from the surface of the peritoneum or from the visceral organs which, as a result of uncontrolled proliferation, tumour cells exfoliate and circulate within the peritoneal fluid.

In colorectal cancer, approximately 5-10% of patients undergoing CRC resection are found to have synchronous peritoneal metastases (e.g. Sadeghi et al, 2000),
whereas a further 20-50% go on to experience metachronous later intraperitoneal cancers (Sadeghi et al, 2000).

In primary tumours of the appendix, the tumour invades through the appendiceal wall or produces a mucocele that eventually ruptures. In both clinical scenarios, mucus-producing adenomatous epithelial cells are disseminated throughout the abdomen and pelvis. This results in extensive accumulation of mucinous tumour at characteristic sites within the peritoneal cavity.

**Survival with Standard Care**

Conventional treatment of colorectal cancer peritoneal metastases involving systemic chemotherapy with or without palliative surgery has a median survival ranging from 5-12.6 months (Sadeghi et al, 2000; Verwaal et al, 2003). Despite relatively bland histology and a better understanding of its aetiology and prognostic features, the long-term survival of patients with PM from appendiceal malignancy remains poor with reported 5-year survival of 50-60% (Hinson et al, 1998).

**Expected numbers of patients in Wales: CRC**

Table 1 shows the incidence rates of CRC in the UK.

Table 1. Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases</th>
<th>Crude Rate</th>
<th>AS Rate</th>
<th>AS Rate - 86% LCL</th>
<th>AS Rate - 86% UCL</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>18,071</td>
<td>10.97</td>
<td>8.62</td>
<td>6.59</td>
<td>10.64</td>
</tr>
<tr>
<td>Female</td>
<td>15,048</td>
<td>9.59</td>
<td>6.49</td>
<td>4.29</td>
<td>9.72</td>
</tr>
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</table>

Based on the persons EASR for Wales of 45.5 – 46.5/100,000 the following calculation was undertaken to derive an estimate of the numbers of patients eligible for consideration of CRS plus HIPEC from colorectal seeding based on the data below:
Population of Wales – 3.1 million (ONS, mid-2012 estimate);
% of peritoneal malignancy secondary to CRC (7-10%);
Peritoneal malignancy as sole site of metastasis (4.3 – 4.8%);
No significant co-morbidity and suitable for assessment (50%);
Informed consent and fit for surgery ratio (1:3 – 1:4)

Thus there are 2 calculated scenarios below based on either actual cases or EASR incident rates:

**Scenario 1: Based on Actual Volumes**

Using a case volume of 2,343 cases per annum, there are expected to be 164 – 234 with PM secondary to CRC. Of these cases, 4.3 – 4.8% would be where PM would be the sole site of metastasis indicating 7 – 11 cases per annum.

Only 50% would have no co-morbidity and would be suitable for referral indicating 3 – 6 cases per annum.

Combining both estimated prevalence and incidence and the natural history of patients currently treated with systemic chemotherapy and palliative surgery, an additional 3-5 patients may be suitable candidates indicating a year 1 case volume of 6 - 11 cases per annum for the whole of Wales. In year 2, this would be expected to drop towards the incident rate (i.e. 3 - 6 cases suitable for surgery for annum).

**Scenario 2: Based on EASR**

Using the incident rate and population of Wales, there are expected to be 1,411 – 1,441 incident cases of CRC per annum in Wales. There would be 7-10% of cases with PM secondary to CRC i.e. 99 – 144 cases. Of these cases 4.3 – 4.8% of cases would be where PM would be the sole site of metastasis indicating 4 – 7 cases per annum.

Only 50% of these cases would have no co-morbidity and suitable for referral indicating 2 – 4 cases.

Combining both estimated prevalence and incidence and the natural history of patients currently treated with systemic chemotherapy and palliative surgery, an additional 3-5 patients may be suitable candidates indicating a year 1 case volume of 5-9 cases per annum for the whole of Wales. In year 2, this would be expected to drop towards the incident rate (i.e. 2-4 cases suitable for surgery for annum).
Expected Costs

The episode costs for CRS plus HIPEC from designated centres is £61,000 at Basingstoke and £70,000 at The Christie, Manchester. Based on these values the expected treatment costs for the cohort* are:

**Scenario 1:**

Year 1 £384,000 – £698,000  
Year 2 £192,000 - £384,000

**Scenario 2:**

Year 1 £323,000 - £576,000  
Year 2 £131,000 - £253,000

*Population proportions taken into consideration (i.e. 2/3rd referred from South Wales to Basingstoke, 1/3rd referred from North Wales to The Christie, Manchester).

**Expected numbers of patients in Wales: Appendiceal**

There is a significant uncertainty in the clinical community in the diagnosis of patients with peritoneal manifestation of disseminated cancer of appendiceal origin.

As a consequence, peritoneal malignancy also covers a different clinical condition that is characterized as a localized or generalized accumulation of abundant gelatinous material within the abdominal and/or pelvic peritoneal cavity associated with a mucinous tumour of the gastrointestinal tract or ovaries - Pseudomyxoma peritonei (PMP).

There is no single definition of PMP. The term is literally interpreted as “false mucinous tumour of the peritoneum”. It is most commonly used for a slowly progressive disease process characterized by extensive mucus accumulation within the abdomen and pelvis. Such a broad definition allows both low grade mucinous adenomas of the appendix and mucus-producing gastrointestinal adenocarcinomas to be included under this entity. Clinically, the term PMP describes a syndrome that produces its symptoms by copious mucus tumour production which results in a “jelly belly”.
Although, in clinical pathology, molecular genetic and immunohistochemical studies the origin of PMP has been studied intensively, there is still confusion about the true origin. Many gynaecological publications have emphasised the association with ovarian mucinous tumour of low malignant potential, also termed mucinous borderline tumour. Standard textbooks have often simply accepted that any mucinous ovarian tumour present in a female represents the origin of the disease. However, when the appendix is examined histologically, mucoceles, adenomas or carcinomas are found in nearly all cases. This simultaneous disease in most female patients might be explained either on the basis of spread from the appendix to the ovary or on the basis of two independent primary disease processes. If there is a single primary neoplasm other deposits should show features consistent with a clonal origin. If there is more than one primary neoplastic lesion a predisposing field change is implied. It has been suggested that this might arise because of mucinous metaplasia due to chronic irritation from ascitic fluid. Despite this controversy, the appendix is still the alleged dominant origin associated with PMP.

Funding for PMP is already established for Specialised Services in Wales for between 2-5 cases per annum. There is considerable uncertainty whether these patients also overlap with the cohorts described by this evidence appraisal or to what extent.

It is therefore uncertain if there will be any increase in the numbers of patients referred for this rare presentation over and above the currently funded number.

**Preoperative diagnostics and patient selection**

Preoperative patient selection plays a pivotal role for the success of CRS and HIPEC regarding clinical as well as oncological patient outcome. Thus, preoperative diagnostics including physical examination, laboratory parameters, tumour markers (CA19-9, CEA, CA125, CA72-4), computed tomography of the chest, abdomen and pelvis with intravenous and oral/rectal contrast and endoscopy with or without endoluminal ultrasonography (colorectal and gastric cancer) are indispensable (Table 2).
Table 2. Preoperative diagnostic workup (Glockzin et al., 2009)

<table>
<thead>
<tr>
<th>Essential preoperative diagnostics</th>
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<tbody>
<tr>
<td>Clinical investigation</td>
</tr>
<tr>
<td>Laboratory testing incl tumor markers</td>
</tr>
<tr>
<td>Computerized tomography (CT) of the chest, abdomen and pelvis with oral, rectal and intravenous contrast</td>
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</tbody>
</table>

<table>
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<tr>
<th>Tumor-specific essential diagnostics</th>
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<tr>
<td>CRC: complete colonoscopy</td>
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<tr>
<td>GC: gastroscopy</td>
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<tr>
<th>Useful additional diagnostics (case-dependent)</th>
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<tr>
<td>Ultrasonography</td>
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<tr>
<td>Magnetic resonance imaging (MRI)</td>
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<tr>
<td>Positron emission tomography (PET)/PET-CT</td>
</tr>
<tr>
<td>Diagnostic laparoscopy</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer, GC: gastric cancer

In some cases additional ultrasound, abdominal magnetic resonance imaging (MRI) and/or PET-CT may be helpful depending on the primary tumour and tumour dissemination. However, some studies have shown that preoperative CT-PCI does not correlate with the intraoperative PCI.

Prognostic Indicators
Quantitative prognostic indicators are essential as clinical guidelines in the selection of treatments to maximise benefits of therapy and to exclude patients who have little or no chance to improve. They are of greatest utility in high risk and costly management protocols. Requirements of a useful quantitative prognostic indicator include reproducibility, prediction of survivorship, and assessment of morbidity and mortality. Prognostic indicators currently in clinical use are shown in Table 3.

Table 3. Quantitative prognostic indicators currently in use in patients with carcinomatosis

<table>
<thead>
<tr>
<th>Tumor histopathology</th>
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</thead>
<tbody>
<tr>
<td>Intraoperative assessment of the extent of carcinomatosis at time of surgical exploration</td>
</tr>
<tr>
<td>• Gilly peritoneal carcinomatosis staging</td>
</tr>
<tr>
<td>• Carcinomatosis staging by the Japanese Research Society for Gastric Cancer</td>
</tr>
<tr>
<td>• Peritoneal Cancer Index (PCI)</td>
</tr>
<tr>
<td>• Dutch Simplified Peritoneal Carcinomatosis Index (SPCI)</td>
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</table>

<table>
<thead>
<tr>
<th>CT PCI</th>
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<table>
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<tr>
<th>Prior Surgical Score</th>
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<table>
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<tr>
<th>Completeness of Cytoreduction Score</th>
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</table>
Gilly Peritoneal Carcinomatosis Staging

The Gilly peritoneal carcinomatosis staging format takes into account the size of lesions found at operation (Table 4). Two advantages of this system are simplicity and reproducibility. The utility of the Gilly staging device in survivorship prediction has been demonstrated in the multi-centric prospective EVOCAPE study which gathered data from 370 patients with peritoneal carcinomatosis from non-gynaecologic malignancies (Sadeghi et al., 2000). A significant difference was observed between stages 1 and 2 with a median survival of 6 months and stages 3 and 4 whose median survival was 3 months. The Gilly carcinomatosis staging has also been validated in patients having combined treatment for carcinomatosis.

Although the Gilly system has been used for almost a decade with acceptable prognostic value, there are some criticisms regarding this system. First, it should not be designated a "staging system" because patients can only be staged once in the course of their disease at the time of diagnosis of the primary malignancy. Usually, a TNM staging system is appropriate. The system might better be called the Gilly prognostic index for carcinomatosis.

A second weakness of the Gilly prognostic index concerns a failure to quantitate distribution of peritoneal surface implants in the stage 3 and 4 categories. Carcinomatosis confined to one portion of the abdomen may carry an excellent prognosis even if the localized tumour implants are of large size. If group III and group IV nodules by size are diffuse throughout the whole abdomen, certainly a much different prognosis would occur. A definitive assessment of not only the size of the nodules but also the distribution of carcinomatosis is necessary for the most accurate assessment of prognosis.

Japanese Research Centre for Gastric Cancer

The Japanese have proposed a quantitation of carcinomatosis that is very simple, has been frequently applied, and has been validated for gastric malignancy. For the original staging a "P factor" is indicated for gastric cancer patients. P-0 means that no carcinomatosis was seen by the surgeon or could be established at the time of surgery. It would currently include patients who are cytology positive for gastric cancer cells. P-1 indicates implants immediately adjacent to the stomach and above the transverse colon. P-2 indicates scattered implants within the abdomen but not of great number. P-3 indicates numerous implants throughout the abdomen and pelvis.

This staging system can also be applied to patients who have carcinomatosis with recurrent gastric cancer. A major deficit of this staging system is its inability to accurately locate the carcinomatosis. Also, it has no size assessment of the cancerous implants. Although the P factor has been of great value historically in the management of primary gastric cancer as peritonectomy and intraperitoneal
Chemotherapy are used for treatment of carcinomatosis, a more precise prognostic assessment is needed to manage gastric cancer peritoneal seeding.

**Peritoneal Cancer Index (PCI)**

The Peritoneal Cancer Index (PCI), like the other carcinomatosis assessments, is determined at the time of surgical exploration of the abdomen and pelvis. With invasive cancer it serves as an estimate of probability of complete cytoreduction and has been found to be an accurate assessment of survival when cytoreductive surgery and perioperative intraperitoneal chemotherapy are used as treatment.

The PCI quantitatively combines the distribution of tumour throughout 13 abdominopelvic regions with a lesion size score. Two transverse and two sagittal planes divide the abdomen into 9 regions. The upper transverse plane is located at the lowest aspect of the costal margin, and the lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into three equal sectors. The lines define 9 regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. Regions 9 through 12 divide the small bowel into upper and lower jejunum and upper and lower ileum (**Figure 5**). To make the PCI tool more quantitative and reproducible, each region is not only defined by the surface landmarks as previously described, but can also be defined by the anatomic structures found in each region (**Table 4**).

**Figure 5. Peritoneal Cancer Index (PCI)**

Peritoneal cancer index (PCI). Two transverse planes and two sagittal planes divide the abdomen into 9 regions. The upper transverse plane is located at the lowest aspect of the costal margin and the
lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into three equal sectors. The lines define the nine regions which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. Regions 9–12 divide the small bowel. Lesion size score is determined after complete lysis of all adhesions and the complete inspection of all parietal and visceral peritoneal surfaces. It refers to the greatest diameter of tumour implants that are distributed on the peritoneal surfaces. Primary tumours or localized recurrences at the primary site that can be removed definitively are excluded from the lesion size assessment. If there is confluence of disease matting abdominal or pelvic structures together, this is automatically scored as L-3 even if it is a thin confluence of cancerous implants.

Table 4. Anatomic structures involved in the 13 abdominopelvic regions of the peritoneal cancer index (PCI).

<table>
<thead>
<tr>
<th>Regions</th>
<th>Anatomic structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Central</td>
<td>Medline abdominal incision – entire greater omentum – transverse colon</td>
</tr>
<tr>
<td>1 Right upper</td>
<td>Superior surface of the right lobe of the liver – undersurface of the right hemidiaphragm – right retro hepatic space</td>
</tr>
<tr>
<td>2 Epiploicum</td>
<td>Retropertitoneal fat pad – left lobe of the liver – lesser omentum – fallopian ligament</td>
</tr>
<tr>
<td>3 Left upper</td>
<td>Undersurface of the left hemidiaphragm – spleen – tail of pancreas – anterior and posterior surfaces of the stomach</td>
</tr>
<tr>
<td>4 Left flank</td>
<td>Descending colon – left abdominal gutter</td>
</tr>
<tr>
<td>5 Left lower</td>
<td>Pelvic sidewall lateral to the sigmoid colon – sigmoid colon</td>
</tr>
<tr>
<td>6 Pelvis</td>
<td>Female internal genitalia with ovaries, tubes and uterus – bladder, Douglas pouch – rectosigmoid colon</td>
</tr>
<tr>
<td>7 Right lower</td>
<td>Right pelvic sidewall – cecum – appendix</td>
</tr>
<tr>
<td>8 Right flank</td>
<td>Right abdominal gutter – ascending colon</td>
</tr>
<tr>
<td>9 Upper jejunum</td>
<td></td>
</tr>
<tr>
<td>10 Lower jejunum</td>
<td></td>
</tr>
<tr>
<td>11 Upper ileum</td>
<td></td>
</tr>
<tr>
<td>12 Lower ileum</td>
<td></td>
</tr>
</tbody>
</table>

The lesion size (LS) score is determined after complete lysis of all adhesions and complete inspection of all parietal and visceral peritoneal surfaces within the abdominopelvic regions. The lesion sizes are then summated for all abdominopelvic regions. The extent of the disease within all regions of the abdomen and pelvis is indicated by a numerical score from 0 to 39.

This quantitative prognostic indicator for colon carcinomatosis established that for patients scoring greater than 20, palliation is the goal of treatment. Currently, a PCI of greater than 20 is regarded as a relative contraindication to an elective intervention for carcinomatosis from colon cancer. It is associated with a low median survival: approximately the same as median survival without surgical intervention. In patients who have a PCI greater than 20, palliative surgery is indicated in order to alleviate symptoms or to prevent symptoms that may occur in the near future. Recent data (Nikolic et al., 2014) have reviewed the prognostic impact of different PCI thresholds. These data have shown that patients with PCI<13 (vs. PCI≥13) have longer OS and DFS which was also confirmed for PCI-subcategories (PCI<7 vs. 7≤PCI<13 vs. PCI≥13).
In an asymptomatic patient with colon carcinomatosis, cytoreductive surgery with intraperitoneal chemotherapy with cure as a goal of treatment is probably not indicated.

An exception to the utility of the PCI is found in treating patients with pseudomyxoma peritonei. Another caveat that must be observed when using the PCI occurs in cases in which a low PCI score is recorded in the presence of invasive cancer at a crucial anatomic site. For example, at exploration one may find invasive tumor in and around the common bile duct with little disease elsewhere. Even though the PCI is low, a complete cytoreduction may not be possible. In these cases, invasive cancer at a crucial anatomic site places the patient into the same category as would systemic metastasis in the lungs or bone. Only palliative surgery is indicated if residual disease post-cytoreduction will be present.

**Dutch Simplified Peritoneal Carcinomatosis Index (SPCI)**

The Simplified Peritoneal Cancer Index (SPCI) was established at the Netherlands Cancer Institute and has been used for colorectal and appendiceal cancer staging (Table 5). This tool has prognostic implication for survival following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

**Table 5. Simplified Peritoneal Carcinomatosis Index (SPCI)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: pelvis</td>
<td>1</td>
</tr>
<tr>
<td>II: right lower abdomen</td>
<td>1</td>
</tr>
<tr>
<td>III: greater omentum, transverse colon and spleen</td>
<td>1</td>
</tr>
<tr>
<td>IV: right subdiaphragmatic area</td>
<td>1</td>
</tr>
<tr>
<td>V: left subdiaphragmatic area</td>
<td>1</td>
</tr>
<tr>
<td>VI: subhepatic and lesser omental area</td>
<td>1</td>
</tr>
<tr>
<td>VII: small bowel and small bowel mesentery</td>
<td>1</td>
</tr>
</tbody>
</table>

Verwaal et al (2003) have provided important information regarding the relationship of the Simplified Peritoneal Cancer Index and the incidence of complications in patients who receive combined treatment. In their review of the toxicity of combined treatment, complications increased when the cancer index recorded involvement of more than five regions (p = 0.044). Also, if the patient had recurrent colon cancer (as opposed to carcinomatosis with primary cancer) or if there was an incomplete cytoreduction, the incidence of complications was significantly higher. Verwaal et al., established that the peritoneal cancer index quantitated not only the survival
outcome of these patients but also the expected morbidity and mortality of the combined treatment (Witkamp et al., 2001).

There are marked similarities between the SPCI and the PCI. Both the anatomic distribution of the tumour masses and the size of the tumour masses within each abdominal region are indicated. In the PCI, there are 13 anatomic sites designated by a diagram; in the Dutch SPCI, there are 7 anatomic regions designated by anatomic site. In both systems the volume of tumor in each region is to be scored quantitatively. Some shortcomings of the SPCI could be formulated. First, the epigastric region, very important in determining the completeness of cytoreduction in some diseases is not designated separately. Disease above the stomach in the lesser omental region may cause the cytoreduction to be incomplete.

A second major criticism of the Dutch SPCI concerns their misuse of their own tool. In their recent publications they perform a survival analysis by SPCI and a toxicity assessment by the SPCI. However, only the involvement of regions 0–7 was indicated. No tumour size in the regions was indicated (Veerwaal et al., 2003; Witkamp et al., 2001).

**Prior Surgical Score (PSS)**

An accepted fact regarding cancer treatment is that the optimal treatment with the highest cure rate, the greatest preservation of function, and the lowest morbidity and mortality is the initial treatment. In the management of carcinomatosis the extent of prior resection before definitive cytoreduction with intraperitoneal chemotherapy has a negative impact on the survival. This occurs because of the cancer cell entrapment phenomenon. Surgery opens tissue planes whose raw surface is a favored site for cancer cell adherence, vascularization and progression. In the use of combined treatment for carcinomatosis, the non-traumatized peritoneal surface is the body's first line of defense against carcinomatosis.

Cancer progression deep to peritoneal surfaces, especially disease imbedded in scar, is difficult or impossible to remove by peritonectomy or to eradicate by intraperitoneal chemotherapy. The prior surgical score (PSS) quantitates the extent of surgery prior to definitive combined treatment. It shows that the greater the surgery the poorer the results of carcinomatosis treatment. The assessment uses a diagram similar to that for PCI but excludes abdominopelvic regions 9–12. For a PSS of 0 no prior surgery or only a biopsy was performed; PSS of 1 indicates one region with prior surgery; PSS-2 indicates 2 to 5 regions previously dissected; PSS-3 indicates more than 5 regions previously dissected. This is equivalent to a prior attempt at complete cytoreduction but in the absence of perioperative intraperitoneal chemotherapy. In appendiceal cancer patients with a prior surgical score of 0–2, the survival using combined treatment was 70% at 5 years; with a prior surgical score of 3, the 5-year survival was 51% (p = 0.001) (Sugarbaker, 1999).
Completeness of Cytoreduction Score (CCS)
The Completeness of Cytoreduction Score functions as a major prognostic indicator for the survival in peritoneal mesothelioma, colon cancer with carcinomatosis, gastric cancer with carcinomatosis and sarcomatosis. CCS is assessed after cytoreductive surgery is completed. Complete cytoreduction (CC-0 or CC-1) or incomplete (CC-2 or CC-3) are determined. A CC-0 is apparent when there is no peritoneal seeding visualized within the operative field. CC-1 indicates nodules persisting after cytoreduction less than 2.5 cm. CC-2 has nodules between 2.5 and 5 cm, whereas a CC-3 indicates nodules greater than 5 cm or a confluence of unresectable tumour nodule at any site within the abdomen or pelvis. The CC-1 tumor nodule size is thought to be penetrable by intra-cavitary chemotherapy and is, therefore, designated as complete cytoreduction if perioperative intraperitoneal chemotherapy is used.

Computerised Tomographic PCI
The preoperative CT is an excellent tool in locating and quantifying mucinous adenocarcinoma within the peritoneal cavity. Unfortunately, with intestinal histologic type of colon cancer the accuracy of the CT is considerably reduced. However, for mucinous carcinomatosis. CT scanning is an accurate prognostic indicator of the possibility of resectability. It may show segmental obstruction of the small bowel or tumour nodules greater than 5 cm on small bowel. Patients who have both of these findings have a likelihood of less than 5% of complete cytoreduction. Obstructed segments of bowel signal an invasive character of malignancy on small bowel surfaces that would be unlikely to be completely cytoreduced.

Large tumour nodules on small bowel or its mesentery are unlikely to be adequately cytoreduced without visceral resection. There are some special demands on CT scanning if the radiologic examination is to be optimized. Bowel loops cut in cross section are often indistinguishable from cancer nodules. Only if maximal oral contrast using a barium sulfate compound is utilized to prepare the patient for this examination can the greatest accuracy and the greatest prognostic implications of the examination be realised.

Another technical requirement is the imaging of solid tumour layered out on the peritoneal surfaces. Unless there is maximal intravenous contrast with a 60 to 120 second delay after contrast infusion will the confluence of malignancy as a thin layer on the peritoneum be imaged. In some patients, the solid tumour, or semi-solid tumour may be distributed to appear as ascites on abdominal and pelvic CT. Much to the surgeon's dismay, upon opening the abdomen, a solid tumour mass filling the abdomen and pelvis and causing adherence of small bowel and small bowel mesentery will be revealed. In this situation, not even palliative surgery can be safely performed. In patients who clinically have a firm abdomen and in whom the surgeon suspects large volume of solid tumour, an ultrasound examination may be required in order to confirm an ascitic versus a solid component of the abdominal and pelvic malignancy. If ultrasound shows that there is only minimal or no ascites and that the
large volume of tumour is solid or semisolid, surgical interventions are not beneficial. It is better to determine the nature of the carcinomatosis radiologically than at the time of a major surgical exploration.

**Description of the intervention**

**Cytoreductive surgery**

CRS consists of numerous surgical procedures depending on the extent of peritoneal tumour manifestation. In appendiceal malignancies, the omental cake, a disseminated tumour infiltration of the greater omentum, represents the most affected abdominal area. Surgery may include parietal and visceral peritonectomy, greater omentectomy, splenectomy, cholecystectomy, resection of liver capsule, small bowel resection, colonic and rectal resection, (subtotal) gastrectomy, lesser omentectomy, pancreatic resection, hysterectomy, ovariectomy and urine bladder resection. In patients with mucinous tumors and infiltration of the umbilicus, an omphalectomy is necessary. Extraperitoneal dissection may enable the anterior parietal peritonectomy and avoid a tumour contamination of the abdominal wall. The extent of intraperitoneal tumour manifestation is determined using the peritoneal cancer index (PCI), a combined numerical score of lesion size (LS-0 to LS-3) and tumour localization (region 0–12). The aim of CRS is to obtain complete macroscopic cytoreduction (CCR-0/1) as a precondition for the application of HIPEC. The residual disease is classified intraoperatively using the completeness of cytoreduction (CCR) score. CCR-0 indicates no visible residual tumour and CCR-1 residual tumour nodules ≤ 2.5 mm. CCR-2 and CCR-3 indicate residual tumour nodules between 2.5 mm and 2.5 cm and > 2.5 cm, respectively.

**Hyperthermic intraperitoneal chemotherapy (HIPEC)**

In case of complete macroscopic cytoreduction (CCR-0/1) CRS is followed by hyperthermic intraperitoneal chemotherapy (HIPEC). The theoretical advantage of the intraperitoneal distribution of cytostatics is a high local concentration of the used agents and reduced systemic toxicity. In vitro studies could show that hyperthermia may potentiate the cytostatic effects. For example an improved tissue penetration could be shown for cisplatin. Moreover, hyperthermia leads to direct cytotoxic effects such as protein denaturation, induction of apoptosis and inhibition of angiogenesis. For the performance of HIPEC one inflow and three outflow drainages are placed sub-phrenically and in the small pelvis. The cytostatic agent is applied via the inflow drainage using a roller pump and heat exchanger in a closed system that allows perfusate circulation (Figure 6).

The intraperitoneal temperature is monitored by two sensors placed in the inflow catheter and in the Douglas pouch. The intraperitoneal temperature should reach 41–42°C leading to an inflow temperature of about 43°C. Until today the cytostatic agents, combinations and concentrations used for HIPEC are not standardized for all peritoneal carcinomatosis centers worldwide. Thus, numerous different protocols are
used for the different tumour entities. The perfusion times ranges from 30 to 120 minutes depending on the protocol and the drug used. Moreover, numerous different drugs and drug combinations are used. HIPEC can be performed in open or closed abdomen technique. One of the leading advantages of the open technique is a better control of the intraperitoneal circulation and uniform distribution of the cytostatic agents. An important disadvantage is the increased risk of contamination compared to the closed abdomen technique. Although a comparison of the existing studies is difficult there seem to be no significant differences between the two techniques regarding morbidity and mortality rates as well as patient survival.

**Figure 6. Schematic diagram of HIPEC procedure**

![HIPEC diagram]

**How the intervention might work**

The administration of HIPEC improves penetration of the chemotherapy, with minimal exposure to the rest of the patient’s body. Heated chemotherapy administered through the HIPEC treatment it is not absorbed by the body in the same way as in traditional systemic chemotherapy; therefore, the more common side effects associated with chemotherapy are not experienced.

This regionally applied heated sterile solution, with chemotherapy, is continuously circulated throughout the abdominal cavity for approximately 90 minutes, and may increase the efficacy of cancer treatment surgery, without causing significant toxicity to the remainder of the body.
Why it is important to do this review

Colorectal cancer is a key public health issue in Wales, accounting for 14% of the total cancer burden. Metastases are the principle cause of death and can occur in 30% of patients at presentation (Cunningham et al, 2010). Usual standard of care for this patient group is conventional surgery combined with systemic chemotherapy. In a prospective study 50 patients with proven peritoneal carcinomatosis of colorectal origin were treated with conventional surgery combined with 5-fluorouracil and leucovorin, or irinotecan in patients treated by 5-fluorouracil within 12 months prior to entry. Survival and progression-free survival were studied and prognostic factors were analysed. The median survival time was 12.6 months. The median time to progression was 7.6 months. Location of primary tumour and result of conventional surgery and systemic chemotherapy were prognostic factors related to survival.

WHSSC reviewed the evidence for clinical and cost effectiveness for CRS and HIPEC in the management of PM in 2011. The review included evidence for all primary seeding tumour sites (e.g. ovarian, gastric, CRC, appendiceal, mesothelial). Following clinical consultation, the view was expressed by the of the Cancer Clinical Effectiveness and Evaluation Group (Peritoneal Malignancy Sub-group) that a repeat review should be conducted focusing on colorectal and appendiceal seeding.

Objectives

The key objectives of this evidence evaluation are summarised below:

- What is the evidence of the clinical effectiveness of CRS plus HIPEC for the treatment of PM of colorectal and appendiceal origin?
- What is the evidence of the cost effectiveness of CRS plus HIPEC for the treatment of PM of colorectal and appendiceal origin?
- What is the evidence for quality of life improvement for CRS plus HIPEC for the treatment of PM of colorectal and appendiceal origin?
- Is there a difference in clinical effectiveness between the different chemotherapy agents used for HIPEC?
- Is there a difference in cost effectiveness between the different chemotherapy agents used for HIPEC?
- Is there a difference in quality of life between the different chemotherapy agents used for HIPEC?
- What is the clinical effectiveness of standard care i.e. systemic chemotherapy plus or minus palliative surgery?
- What is the cost effectiveness of standard care i.e. systemic chemotherapy plus or minus palliative surgery?
- What is evidence for quality of life improvement of standard care i.e. systemic chemotherapy plus or minus palliative surgery?
- What is the safety of CRS plus HIPEC in the treatment of PM?
- What is the recurrence rate following CRS and HIPEC in PM?
- What prognostic scoring systems are available to predict outcomes of CRS and HIPEC in PM?
Methods

Criteria for considering studies for this review
Selection criteria and data collection and analysis

Search methods
The medical literature was searched to identify studies and reviews relevant to CRS plus HIPEC or SC (systemic chemotherapy plus conventional surgery) for the treatment of PC colorectal and appendiceal seeding). Searches were conducted of the following databases, covering the period from their commencement to 25-09-2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the initial searches. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

Study Characteristics

Criteria

Publication type
Clinical studies were included. Emphasis was placed on identifying good quality studies.

Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.

Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.

Patients
Adults (>18 years), with peritoneal malignancy of colorectal or appendiceal origin (not defined as PMP)

Intervention
HIPEC and CRS or standard surgery and systemic chemotherapy

Outcome
Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy and/or quality of life and/or cost effectiveness.

Language
Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.
The outcome measures assessed were:

- Overall Survival,
- Progression free survival;
- Mortality;
- Procedural complications;
- Completeness of CRS;
- Adverse events;
- Recurrence;
- Quality of life;
- Cost effectiveness

Primary outcomes

- Overall survival;
- Progression free survival;
- Mortality

Secondary outcomes

- Procedural complications;
- Completeness of CRS;
- Adverse events;
- Toxicity;
- Recurrence;
- Quality of life;
- Cost effectiveness

Search methods for identification of studies

**Electronic searches**

**Searching other resources**

Clinical audit data was requested from UK centres treating patients for PC using HIPEC and CRS.

Data collection and analysis

**Selection of studies**

Included studies had to provide data on the outcome measures identified under *Types of Outcome Measures* in adults (>18 years) with >10 patients recruited to the
study with a histologically confirmed diagnosis of PC or either colorectal or appendiceal origin undergoing treatment with CRS plus HIPEC or standard of care (conventional surgery plus systemic chemotherapy).

Data extraction and management

Data were extracted by two reviewers using data extraction forms developed *a priori* with any discussions and study assessments for inclusion discussed with the Cancer CEGG Sub-Group on HIPEC and CRS as a third reviewer (Chair Dr Richard Adams, Oncologist, Velindre Cancer Centre).

The quality of the studies and grades of evidence included were assessed using recognised quality assessment tools provided by the Cochrane Collaboration (e.g. GRADEPro and RevMan).

Assessment of risk of bias in included studies

Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.

- An assessment of the validity of studies included in a Cochrane review should emphasise the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.
- The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a judgement and a support for the judgement for each entry in a ‘Risk of bias’ table, where each entry addresses a specific feature of the study. The judgement for each entry involves assessing the risk of bias as ‘low risk’, as ‘high risk, or as ‘unclear risk’, with the last category indicating either lack of information or uncertainty over the potential for bias.
- Plots of ‘Risk of bias’ assessments were created in RevMan and highlighted in this evaluation.
- In clinical trials, biases can be broadly categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories.
- For parallel group trials, the features of interest in a standard ‘Risk of bias’ table of a Cochrane review are sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.

Measures of treatment effect

Measures were calculated or reported in a standard manner through this review. Both absolute and relative risk have been reported.
Dealing with missing data

Where known missing data was recorded in the full title analysis, this was recorded in the summary of characteristics (Appendix 1). If there was no mention in either study abstract or full title analysis, this was recorded as unknown. If the amount of missing data >10% of the treatment population, the study was excluded from the analysis.

Assessment of heterogeneity

If confidence intervals for the results of individual studies (generally depicted graphically using horizontal lines) have poor overlap, this generally indicates the presence of statistical heterogeneity. More formally, a statistical test for heterogeneity is available. This chi-squared ($\chi^2$, or Chi$^2$) test is included in the forest plots in this evidence review. It assesses whether observed differences in results are compatible with chance alone. A low P value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance).

Care must be taken in the interpretation of the chi-squared test, since it has low power in the (common) situation of a meta-analysis when studies have small sample size or are few in number. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance. A further problem with the test, which seldom occurs in Cochrane reviews, is that when there are many studies in a meta-analysis, the test has high power to detect a small amount of heterogeneity that may be clinically unimportant.

Some argue that, since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable. Thus the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity will always exist whether or not we happen to be able to detect it using a statistical test. Methods have been developed for quantifying inconsistency across studies that move the focus away from testing whether heterogeneity is present to assessing its impact on the meta-analysis.

Thresholds for the interpretation of $I^2$ can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of $I^2$ depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for $I^2$).
# Results

## Results of the search

The research strategy was undertaken using a predefined primary protocol for rapid literature review by Public Health Wales. Subsequent to this, hand searching of relevant articles was also undertaken as part of the protocol. The predefined search strategy identified a total of 355 potentially relevant publications. Following screening of abstracts and titles, 283 articles were excluded leaving 72 articles retrieved for full text. Five additional articles were additionally provided via manual searches giving 77 articles to detailed assessment. Of these 38 were excluded leaving 39 studies for assessment. **Figure 7** provides an outline of the search strategy.

**Figure 7. Flow diagram summarising flow strategy**

<table>
<thead>
<tr>
<th>Identification</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articles Identified through database searches n=355</td>
<td>Articles excluded after screening titles and abstracts n=283 including:</td>
</tr>
<tr>
<td></td>
<td>• Reviews</td>
</tr>
<tr>
<td></td>
<td>• Consensus statements/editorials and letters</td>
</tr>
<tr>
<td></td>
<td>• Other cancer subtypes</td>
</tr>
<tr>
<td></td>
<td>• Lack of required data</td>
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<table>
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<th>Eligibility</th>
<th>Inclusion</th>
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<tbody>
<tr>
<td>Number of full titles assessed of eligibility n=72</td>
<td>Total number studies for review n=39</td>
</tr>
<tr>
<td></td>
<td>Articles excluded after screening titles and abstracts n=38 including:</td>
</tr>
<tr>
<td></td>
<td>• Studies &lt; 10 patients;</td>
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<tr>
<td></td>
<td>• Duplicate data</td>
</tr>
<tr>
<td></td>
<td>• Other cancer subtypes</td>
</tr>
<tr>
<td></td>
<td>• Predominantly other cancer sub-types</td>
</tr>
</tbody>
</table>

| Manual searches n=5 | Total number of titles chosen for full text review n=77 |

<table>
<thead>
<tr>
<th>Identification</th>
<th>Screening</th>
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<tbody>
<tr>
<td>Articles Identified through database searches n=355</td>
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<td></td>
<td>• Other cancer subtypes</td>
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<td></td>
<td>• Lack of required data</td>
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</tbody>
</table>
Description of studies

**Appendiceal Sub-group**

The literature review identified two case studies analysing CRS plus HIPEC in appendiceal patients (Glehen et al., 2004b; Omohwo et al., 2009) with high-grade appendiceal neoplasm. A review of PMP was outside the scope of this evidence review.

Appendiceal subgroups were components of data presented in other case series described under the section for the colorectal sub-group and Appendix 1 identifies studies which included patients with appendiceal tumours.

In Glehen et al., 2004b, 645 patients with the diagnosis of an epithelial peritoneal surface malignancy of appendiceal origin were treated with a curative intent using a standardized management plan with cytoreductive surgery and perioperative intraperitoneal chemotherapy (PIC). This group of patients represents a single surgeon’s complete operative experience with this disease during this period of time with no patients eliminated from the data analysis. No patients were lost to follow-up.

**Patient selection**

A total of 174 of these patients (27%) underwent an incomplete cytoreductive surgery and had residual tumour nodules more than 0.25 mm after surgery. A statistical analysis of these 174 patients constitutes the basis of the study, focused on survival and the impact of prognostic factors on survival.

**Overall Treatment Strategy**

The treatments used in a curative approach to appendiceal malignancy involved 2 major components. The intent of treatment of all patients was maximal surgery combined with maximal regional chemotherapy, and these 2 therapies were blended together into a single treatment plan. Using extensive electrosurgery, 1 to 6 peritonectomy procedures and appropriate gastrointestinal resections were performed in an attempt to remove all visible tumour. Intraperitoneal chemotherapy was withheld perioperatively if small bowel loops could not be separated to allow intraperitoneal access to a majority of peritoneal surfaces. This perioperative intraperitoneal chemotherapy was supplemented postoperatively by additional cycles of combined intraperitoneal and systemic chemotherapy.
Chemotherapy

Of the 174 patients, 37 patients did not receive perioperative intraperitoneal chemotherapy because of the impossibility to achieve near complete separation of bowel loops. The remaining 137 patients received perioperative intraperitoneal chemotherapy with mitomycin C and 5-fluorouracil. Before March 1993, patients were given normothermic mitomycin C as early postoperative intraperitoneal chemotherapy (EPIC) on postoperative day 1 at a dose of 12.5 mg/m² for males and 10 mg/m² for females. The 5-fluorouracil has always been given at 650 mg/m² on postoperative days 2 to 6 or 1 to 5.18 Seventy-six received EPIC. As hyperthermic intraoperative chemotherapy became available after March 1993, the same dose of mitomycin C was given in the operative room with 41 to 42°C heat and manual distribution of the chemotherapy solution.18 Sixty-one patients were given IPCH. This was given in the absence of 5-fluorouracil in 11 patients if there was a high risk for fistula formation. Intraperitoneal chemohyperthermia was combined with EPIC 5-fluorouracil in 50 patients.

Twenty-four patients had been previously treated with intraperitoneal chemotherapy and 56 patients with systemic chemotherapy. Thirty-three patients also received 3 cycles of combined intravenous mitomycin C and intraperitoneal 5-fluorouracil at monthly intervals postoperatively. Fifty-six patients received postoperative systemic chemotherapy as clinically indicated with various regimens involving 5-fluorouracil, leucovorin, oxaliplatin, mitomycin C, paclitaxel, irinotecan, and cisplatin. The information regarding preoperative and adjuvant chemotherapy was incomplete; a great majority of the systemic chemotherapy treatments were not given at our institution.

Results

Of the 645 patients treated for peritoneal surface spread of an appendiceal malignancy, 174 (27%) underwent an incomplete cytoreductive surgery: 37 patients underwent a CC-2 resection and 137 a CC-3 resection. There were 99 males and 75 females with a mean age of 52.7 years (range 19–88). Forty-eight patients had a PSS of 0 to 2, and the other 126 patients had a PSS of 3. The median survival of these 174 patients was 20.5 months and their overall 2-year, 3-year, and 5-year survivals were 42.8%, 34%, and 15.3%. The Kaplan-Meier survival distribution is shown in Figure 8.
Figure 8. Kaplan-Meier survival distribution for 174 patients treated by incomplete cytoreductive surgery. Survival was computed from the initial cytoreduction Glehen et al., 2004b.

for patients who did not receive perioperative intraperitoneal chemotherapy \((P <0.001)\). The Kaplan-Meier survival distribution for these 4 groups of patients is shown in Figure 9. The 61 patients treated by IPCH had a median survival of 39.4 months compared with 18.1 month for the 113 patients treated without IPCH \((P < 0.001)\). The 126 patients treated with EPIC had a median survival of 20.9 months compared with 18 months for patients treated without EPIC. The survival difference was not significant \((P =0.589)\).
Figure 9. Kaplan-Meier survival distribution for 137 patients treated by incomplete cytoreductive surgery according to the type of perioperative intraperitoneal chemotherapy. Survival was computed from the initial cytoreduction performed. IPCH, intraperitoneal chemohyperthermia; EPIC, early postoperative intraperitoneal chemotherapy.

Survival by Number of Operative Procedures

Of these 174 patients, 141 underwent 1 operative intervention with a median survival of 18.1 months. Thirty-three patients (19%) treated with more than 1 operative intervention had a median survival of 36.8 months ($P < 0.003$). Patients were selected for additional attempts of combined treatment by clinical criteria. If there was systemic disease, reoperation was not performed. If the preoperative computed tomography (CT) of the abdomen and pelvis showed recurrent disease diffusely layering on small bowel, effective debulking was thought to be impossible and reoperation was not performed. The performance status of the patient was also considered. The Kaplan-Meier survival distribution for patients based on number of operative interventions is shown Figure 10. Twenty-eight of these 33 patients had 2 operative interventions.
Figure 10. Kaplan-Meier survival distribution based on number of operative interventions. Survival was computed from the initial cytoreduction performed.

Figure 11. Kaplan-Meier survival distribution based on the morphologic type of the tumour. Survival was computed from the initial cytoreduction performed at our institution.
Survival by Assessment of Tumour Histology

Forty-one patients had disseminated peritoneal adenomucinosis with a median survival of 30.8 months, 64 patients had a hybrid type with a median survival of 20.1 months, and 69 patients had mucinous adenocarcinoma with a median survival of 16.4 months (P < 0.001). The Kaplan-Meier distribution of these 3 groups of patients is shown in Figure 11. Thirty-six patients presented with signet ring cells on histopathologic examination. The presence of signet ring cells had a significantly negative influence on survival (P <0.004) (Figure 12). Lymph node involvement was observed in 22 patients and also had a significantly negative influence on survival (P < 0.001) (Figure 12). No patient with lymph node involvement was alive at 2 years.

Other statistical evaluations including age, gender, PSS, CC score, treatment versus no treatment with preoperative systemic chemotherapy, preoperative intraperitoneal chemotherapy, long-term postoperative intraperitoneal chemotherapy, and adjuvant systemic chemotherapy did not have a significant impact on survival.

Multivariate Analysis

By multivariate analysis, the presence of signet ring cells, lymph node involvement, the number of procedures performed, and the use of hyperthermia were the variables that had a significant influence on survival (P <0.047, P <0.001, P < 0.018, and P <0.001, respectively).
Morbidity and Mortality

The information concerning morbidity and mortality was prospectively recorded since 1998 and was available on 69 patients. Grade III/IV postoperative complications (National Cancer Institute Common Toxicity Criteria) occurred in 23 (33.3%) of these patients. Two patients suffered combined grade III/IV complications. The most frequent complication was systemic sepsis and was due to urine infection in 6 of 7 cases. There were no postoperative intestinal fistulas. Three patients required a return to the operative room: 1 for postoperative intra-abdominal bleeding and 2 for urine leaks. There was no postoperative death. The postoperative complications are summarized in Table 6.

Table 6. Morbidity and Mortality of 69 Consecutive Treatments Combining Incomplete Cytoreductive Surgery With Perioperative Intraperitoneal Chemotherapy, Prospectively Recorded

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic sepsis</td>
<td>7</td>
<td>10.1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4</td>
<td>5.8</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>4</td>
<td>5.8</td>
</tr>
<tr>
<td>Hematological toxicity</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Urine leak</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Neurological toxicity</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Cardiovascular toxicity</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Line sepsis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Wound sepsis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Combined grade III/IV morbidity</td>
<td>23</td>
<td>33.3</td>
</tr>
<tr>
<td>Treatment-related mortality</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Authors’ conclusion

Incomplete cytoreduction plus perioperative intraperitoneal chemotherapy of peritoneal dissemination from appendiceal malignancy results in limited long-term survival. Patients with signet ring histology or lymph node involvement have an especially poor outcome. Repeat cytoreduction and intraperitoneal chemohyperthermia may improve outcome.

WHSSC Commentary

It is difficult to define the optimal management of peritoneal surface malignancy from appendiceal mucinous tumours because of a lack of controlled studies, difficulty with
uniform histologic classification, and the rare nature of this entity. In addition, the long natural history makes prolonged follow-up necessary to determine the impact of therapeutic intervention. Compared to colon cancer, appendiceal mucinous tumors with peritoneal spread possess a unique tumour biology characterised by a paucity of dissemination to lymph nodes, liver, or systemic sites; this makes them amenable to aggressive local-regional treatment.

In Omohwo et al., 2009, a retrospective study of a prospective database of 56 patients (from 1999 to 2007) with appendiceal neoplasms treated with CRS and HIPEC was carried out. Histology of the disease, CC score, and peritoneal cancer index (PCI) score were assessed independently and collectively for each group of patients. Survival analysis was performed using the Cox proportional hazard model.

Results

Three-year overall survival was 60%. The median peritoneal cancer index score was 25 or higher. Survival analysis by tumour histology was 80% for patients with low-grade tumours and 52% for patients with high-grade tumours (p = 0.024). Survival by completeness of cytoreduction was 78% for patients with a low CC score (0 to 1) and 28% in patients with a high CC score (2 to 3; p = 0.01). There was no statistically significant difference in survival between the low-grade and high-grade tumours when a complete cytoreduction was performed in both groups of patients: 80% versus 68% (p = 0.69).

Authors’ conclusion

CRS and HIPEC is an effective treatment for patients with disseminated appendiceal tumours. High-grade tumours also benefit from this approach and should not be excluded from CRS and HIPEC. Every effort should be made to achieve a complete cytoreduction regardless of the tumour histology.

WHSSC Commentary

This is a small, comparative observational study comparing low-grade and high grade tumours. Although there was no statistical difference in survival between low and high grade tumours, the study lacks power to determine the true effect sizes in each group.

Colorectal Sub-group

Systematic Review and Meta-analysis

Three systematic reviews were identified using data from randomised controlled trials and comparative case series data (n= 5,435). The review question was clearly stated in each study and inclusion criteria were defined for participants, intervention and outcomes. Survival was the key primary outcome for all three of the reviews; secondary outcomes included disease status, morbidity, mortality, blood loss,
operative duration, hospital stay, prognostic factors and quality of life. Completeness of cytoreduction was also assessed in two of the three systematic reviews using the Completeness of Cytoreduction Score (CCR Score).

**In Yan TD et al., (2006),** published studies on CRS and HIPEC for CRPC were identified by searching the MEDLINE database (1966 to March 2006), EMBASE (1988 to March 2006), PubMed (January 1980 to March 2006), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Review of Effectiveness (DARE; up to March 2006). The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Expert academic surgeons in Washington, DC, were asked whether they knew about any unpublished data. All relevant articles identified were assessed with application of predetermined selection criteria.

**Selection Criteria**

All the patients had peritoneal carcinomatosis from colorectal origin confirmed by pathologic examination. Patients who were diagnosed with peritoneal dissemination from appendiceal neoplasms were excluded, as these patients have a significantly better prognosis than non-appendiceal colorectal cancer. Studies using the combined treatment modality of CRS and PIC were evaluated. Studies reporting the effectiveness of CRS and PIC for tumours without specific documentation of CRPC were excluded.

CRS consisted of peritonectomy procedures (anterior parietal peritonectomy, omentectomy-splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, and lesser omentectomy with stripping of the omental bursa-cholecystectomy) and visceral resections (rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy, and small bowel resection).

The type and extent of peritonectomy procedures were not uniformly performed in all the studies included. PIC regimens included IPHC and/or early postoperative intraperitoneal chemotherapy (EPIC) within 7 days of surgery. The combination of intraperitoneal chemotherapy used in the operating room with hyperthermia has been referred to by many different nomenclatures: IPHC, heated intraoperative intraperitoneal chemotherapy (HIIC), hyperthermic intraperitoneal chemotherapy (HIPEC), or continuous hyperthermic peritoneal perfusion (CHPP). In this review, IPHC was the designated terminology.
Table 7. Literature review from Yan TD et al., 2009

<table>
<thead>
<tr>
<th>Treatment Center</th>
<th>Evidence</th>
<th>Year</th>
<th>Median Follow-Up (months)</th>
<th>No. of Patients</th>
<th>IPHC</th>
<th>EPIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Level 1</td>
<td>2003</td>
<td>22</td>
<td>54</td>
<td>MMC</td>
<td>—</td>
</tr>
<tr>
<td>Villegui&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Level 1</td>
<td>2004</td>
<td>52</td>
<td>16</td>
<td>—</td>
<td>MMCFU</td>
</tr>
<tr>
<td>Uppsala&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Level 3</td>
<td>2004</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td>FU</td>
</tr>
<tr>
<td>Multi-institutional&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2001</td>
<td>63</td>
<td>506</td>
<td>Various regimens</td>
<td>± FU</td>
</tr>
<tr>
<td>Washington&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2006</td>
<td>60</td>
<td>70</td>
<td>MMC</td>
<td>FU</td>
</tr>
<tr>
<td>Lyon&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2004</td>
<td>60</td>
<td>59</td>
<td>MMC</td>
<td>—</td>
</tr>
<tr>
<td>Villegui&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2006</td>
<td>55</td>
<td>30</td>
<td>LOHP</td>
<td>—</td>
</tr>
<tr>
<td>Amsterdam&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2005</td>
<td>46</td>
<td>117</td>
<td>MMC</td>
<td>—</td>
</tr>
<tr>
<td>Whiston-Sallitt&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2004</td>
<td>15</td>
<td>77</td>
<td>MMC</td>
<td>—</td>
</tr>
<tr>
<td>Rome&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2000</td>
<td>—</td>
<td>14</td>
<td>MMC + cisplatin</td>
<td>—</td>
</tr>
<tr>
<td>Columbus&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Level 4</td>
<td>1996</td>
<td>10</td>
<td>16</td>
<td>MMC</td>
<td>—</td>
</tr>
<tr>
<td>Padova&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2003</td>
<td>15</td>
<td>46</td>
<td>MMC + cisplatin</td>
<td>—</td>
</tr>
<tr>
<td>Bolgaro&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2005</td>
<td>21</td>
<td>18</td>
<td>MMC</td>
<td>FU</td>
</tr>
<tr>
<td>Sydney&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Level 4</td>
<td>2005</td>
<td>12</td>
<td>30</td>
<td>MMC</td>
<td>FU</td>
</tr>
</tbody>
</table>

Abbreviations: EPIC, early postoperative intraperitoneal chemotherapy; IPHC, intraperitoneal hyperthermic chemotherapy; CRS, cytoreductive surgery; MMC, mitomycin; FU, fluorouracil; LOHP, oxaliplatin.

Assessment of study quality

The authors reported a formal validity assessment (see Table 7). The review described one RCTs, two non-randomised comparative study and 11 observational studies without control groups including one multi-centre study. The RCT (Veerwaal et al., (2003)) compared standard treatment with palliative surgery followed by systemic chemotherapy to a combined treatment using CRS plus HIPEC followed by the same systemic chemotherapy. The RCT was successfully completed with the treatment allocated by appropriate process for concealed randomisation. The two arms were similar in terms of baseline characteristics and eligibility criteria were specified (for more details see section on RCTs).

Methods of synthesis

Studies were grouped by study design (comparative or observational). Pooled HRs with 95% CIs were calculated for overall survival using data from comparative studies for 1-, 2-, 3- and 5-year survival (Table x). The data reported a consistent 9 – 18 months improvement in median survival for CRS plus HIPEC vs. SC alone and that patients receiving complete cytoreduction had a much improved prognosis, achieving a median survival of 28 to 60 months and 5-year survival of 22% to 49%.
The review also presented data on morbidity. Nine studies reported perioperative outcomes (Table 8). The overall morbidity rate varied from 23% to 44%. Haematologic toxicity varied from 2.4% to 19%. The median blood loss was 940mL to 3,900 mL. The median operation duration was 5.5 to 9.0 hours. Four to 11% of patients returned to the operating theatre for management of postoperative complications. Overall mortality ranged from 0% to 12%. The median and mean hospital stay varied from 10 to 29 days and 11 to 14 days respectively (Table 9). Bed acuity was not reported.

Table 9. Morbidity and mortality of CRS with HIPEC with or without early post-operative intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis (Yan TD et al., 2009).
Data Extraction

Two reviewers independently appraised each included article using a standard form and extracted data on methodology, quality criteria and outcomes. Meta-analysis was not undertaken because only three studies included a comparator and there was heterogeneity in treatment regimens. Clinical effectiveness was synthesised that narrative review with full tabulation of results of all included studies.

Authors’ conclusions

The current evidence suggests that CRS plus HIPEC is associated with improved survival and compared with systemic chemotherapy for peritoneal carcinomatosis from colorectal carcinoma.

WHSSC commentary

The review question was clearly stated and inclusion criteria were defined for participants, intervention and outcomes. Criteria for study design were broad. Two reviewers were involved in some aspects of data extraction, which minimised reviewer error and bias; it was unclear whether similar methods were used for study selection and the entire data extraction process. Study validity was formally assessed and so results from these studies and any synthesis were graded. Data from RCTs and non-randomised studies were not pooled so effect sizes were estimated. The evidence that was based on a small number of studies with different designs suggests that the authors’ conclusions should be interpreted with caution.

In Cao et al., (2009), studies that evaluated cytoreductive surgery, hyperthermic perioperative intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy or combinations of these interventions in patients with histologically defined colorectal peritoneal carcinomatosis were eligible for inclusion. Studies in which more than 20% of patients had peritoneal carcinomatosis of appendiceal origin and studies that did not specify that tumours were of colorectal origin were excluded unless data regarding CRCP patients were presented separately. Case studies and studies with fewer than 10 patients were excluded.

The review assessed overall survival (defined as the time from surgical intervention to death or end of follow-up) yearly up to five years post intervention. The review also assessed median survival, morbidity rates and hospital stay.

Included studies evaluated different combinations of specified peritonectomy procedures and different chemotherapy regimens (details were reported). Studies used different criteria to select patients; some included patients with lymph node and/or liver metastases. Duration of follow-up ranged from 10 to 113 months.
The authors stated that two reviewers independently reviewed each study and resolved disagreements by discussion; it was unclear whether this referred to study selection.

**Assessment of study quality**

The authors did not report a formal validity assessment. However, they discussed the quality of included randomised controlled trials (RCTs) in the text and classified studies using the hierarchy of evidence described by the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The authors did not state how many reviewers classified studies.

**Data extraction**

Where possible, for each study the percentages of patient who survived one, two, three, four and five years were extracted together with the median survival, mortality and morbidity rates and duration of hospital stay. Hazard ratios (HR) with 95% confidence intervals (CIs) of survival were extracted or calculated.

The authors stated that two reviewers independently extracted survival rates from survival curves. In addition, two reviewers independently reviewed each study and resolved disagreements; it was unclear whether this referred to data extraction.

**Methods of synthesis**

Studies were grouped by study design (comparative or observational). Pooled HRs with 95% CIs were calculated for overall survival using data from comparative studies. Heterogeneity was assessed using $\chi^2$ and $I^2$ statistics. For observational studies, overall mean survival rates were calculated for one two, three, four and five years and the range of perioperative morbidity rates and duration of hospital stay were reported.

**Results of the review**

Forty-seven studies were included (n=3,941): two RCTs (n=140); two comparative studies (n=114); and 43 observational studies (n=3,687).

**Comparative studies:**

One RCT reported adequate concealed methods of stratified randomisation, baseline comparability of treatment groups and analysis on an intention-to-treat basis. The other RCT failed to recruit the intended number of patients and treatment groups appeared non-comparable at baseline.

Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy was associated with a statistically significant improvement in survival compared with control (HR 0.55, 95% CI 0.40 to 0.75; four studies, n=271).
Cytoreductive surgery in combination with hyperthermic perioperative intraperitoneal chemotherapy was associated with a statistically significant improvement in survival compared with palliative care (HR 0.47, 95% CI 0.32 to 0.69; two studies, n=201).

There was no statistically significant difference in survival between cytoreductive surgery plus early postoperative intraperitoneal chemotherapy plus systemic chemotherapy compared to surgery plus systemic chemotherapy (two studies, n=70). There was no significant heterogeneity for any analysis.

Observational studies:

Overall median survival ranged from 11.9 to 60.1 months. Median survival rates were 76% at one year, 55% at two years, 36% at three years, 28% at four years and 19% at five years. Perioperative morbidity rates ranged from 14.8% to 76% and perioperative mortality ranged from 0% to 12%. Average duration of hospital stay ranged from nine to 29 days.

Authors’ conclusions

Cytoreductive surgery in combination with perioperative intraperitoneal chemotherapy significantly improved survival compared with control in patients with colorectal peritoneal carcinomatosis.

WHSSC commentary

The review question was clearly stated and inclusion criteria were defined for participants, intervention and outcomes. Criteria for study design were broad. Limiting the search to English-language studies identified in one database plus references raised the potential for publication and language biases and may have resulted in the omission of other relevant studies. Two reviewers were involved in some aspects of data extraction, which minimised reviewer error and bias; it was unclear whether similar methods were used for study selection and the entire data extraction process. Study validity was not formally assessed and so results from these studies and any synthesis may not be reliable. Data from RCTs and non-randomised studies were pooled using meta-analysis; pooling studies with different design is questionable. The limited search and evidence that was based on a small number of studies with different designs suggests that the authors’ conclusions should be interpreted with caution.

In Mirnezami et al., (2014), an electronic literature search was carried out using MEDLINE (1965—September 2013), EMBASE (1980—September 2013), CINAHL (1982—September 2013), and the Cochrane Library databases. The following medical subject heading terms and key words were used: ‘colorectal cancer’; ‘peritoneal’; ‘carcinomatosis’; ‘cytoreductive surgery’; ‘chemotherapy’; ‘intraoperative’; and ‘intraperitoneal’. The ‘related articles’ function was used to broaden the search and all abstracts, studies and citations retrieved were scanned for subject relevance. The latest date of this search was January 2014. All potentially
relevant publications were retrieved in full text and formally evaluated for study inclusion. Reference lists of all relevant publications were hand-searched for additional studies missed by the search strategy, and this method of cross-referencing was continued until no further relevant publications were identified.

**Assessment of study quality**

Study methodology was carried out in accordance with the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) recommendations for improving the standard of systematic reviews. Included studies had to provide comparative survival outcome data in >15 male/female adult patients (>18 years) with a histologically confirmed diagnosis of primary or recurrent CPM undergoing treatment with either CRS plus HIPEC or SC alone.

Studies reporting comparative outcomes for cancer subtypes other than colorectal were only included if survival outcome data were reported independently for CPM cases. Only English language publications were included. Two reviewers (RM and AHM) independently extracted the following data from all eligible studies according to a predetermined protocol: First author, year of publication, study location, study type, study time frame, population characteristics, number of subjects, primary or recurrent disease, stage of CPM (peritoneal cancer index (PCI) or alternative scoring method for disease extent), chemotherapeutic regimen, details of previous treatment (chemotherapy/radiotherapy), follow-up duration, incidence of morbidity and mortality, completeness of cytoreduction (CCR, CCR score and/or R-classification where reported), and 2- and 5-year survival (overall and/or disease-free).

Data from studies including mucinous appendiceal tumours were excluded, unless the data were separately evaluable. Extracted data were entered into a computerised database and cross-checked to reach consensus. Included studies were subjected to an assessment of methodological quality and validity and graded on strength of evidence using the revised grading system of the Scottish Intercollegiate Guidelines Network.

**Data extraction**

Statistical analysis was performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA) to derive odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for 2- and 5-year survival with CRS+ HIPEC vs SC alone. Between-study heterogeneity was assessed using Cochran’s Q-test and further quantified using the I² statistic. The Q-statistic is underpowered and therefore homogeneity of studies was assumed at a P-value greater than 0.1.

**Methods of synthesis**

Overall pooled OR for 2- and 5-year survival with 95% CI was calculated using the fixed-effect model (FEM), in the absence of significant study heterogeneity. The relative weight conferred to each study is inversely proportional to the variance associated with the OR and is represented by squares in the forest plots. The pooled estimate is represented by a diamond in the forest plots, the width of which...
corresponds to the 95% CI. Publication bias was assessed visually with funnel plots and Egger’s regression test.

Results of the review

Three case–control studies (Mahteme et al, 2004; Elias et al, 2009; Franko et al, 2010) and one RCT (Verwaal et al, 2008) published between 2004 and 2010 met the inclusion criteria and were included in the meta-analysis. The included studies comprised a total of 342 patients with CPM, of whom 187 were treated with CRS plus HIPEC and 155 received standard treatment with SC alone.

In three of the studies HIPEC was administered intra-operatively, commencing immediately after CRS (Verwaal et al, 2008; Elias et al, 2009; Franko et al, 2010) with duration of treatment ranging from 30 to 100 min. In one study, intraperitoneal chemotherapy was administered from the first postoperative day onwards (early postoperative intraperitoneal chemotherapy, EPIC) for a variable duration (Mahteme et al, 2004). The intraperitoneal chemotherapeutic agent was mitomycin C (MMC) in two of the studies (Verwaal et al, 2008; Franko et al, 2010). Elias et al (2009) used a bidirectional protocol consisting of intraperitoneal Oxaliplatin and intravenous 5-fluorouracil (5-FU) and Leucovorin. Mahteme et al (2004) administered IV Leucovorin 60 min into the initiation of intraperitoneal chemotherapy with 5-FU. In the study by Verwaal et al (2008) 105 patients with CPM were randomised to SC alone (5-FUþLeucovorin; n=51) or CRSþHIPEC (MMC; n=54) treatment arms. Importantly, all patients in the CRS plus HIPEC group received adjuvant chemotherapy (5-FUþLeucovorin). The study by Elias et al (2009) compared outcomes following CRSþHIPEC (n=48) and SC alone for treatment of CPM. All patients in the CRSþHIPEC treatment arm received neoadjuvant (NA) chemotherapy, and only patients who demonstrated no evidence of disease progression after 3–4 months of NA therapy were included.

Patient selection

The primary indication for treatment was defined as the presence of peritoneal metastases of colorectal origin in all four of the studies included. Age as a means of patient selection was restricted to >75 years (Mahteme et al, 2004), >71 years (Verwaal et al, 2008), and >66 years (Elias et al, 2009) in different studies. Patients with ‘extensive’ and/or ‘significantly symptomatic’ CPM were deemed ineligible for study enrolment in two of the studies (Mahteme et al, 2004; Elias et al, 2009). More precise definitions were not provided with respect to assessment of resectability in these two studies. Patients with lung/liver metastases or other extra-abdominal disease were excluded in two studies (Mahteme et al, 2004; Verwaal et al, 2008), whereas two studies included patients with limited liver metastases (Elias et al, 2009; Franko et al, 2010).

Three of the studies only included patients deemed to be of good general functional status (Mahteme et al, 2004; Verwaal et al, 2008; Elias et al, 2009). This classification was further defined in only two of the studies, with normal bone marrow indices and renal and liver function tests regarded as components of the eligibility
criteria for one study, whereas an American Society of Anaesthesiology score of 1 or 2 was regarded as inclusion criteria for another of the studies included in this meta-analysis (Mahteme et al, 2004; Verwaal et al, 2008). Study recruitment was restricted to patients aged 75 years (Mahteme et al, 2004), 71 years (Verwaal et al, 2008), and 66 years (Elias et al, 2009) in different studies.

**Survival**

Survival outcome data are summarised in **Figure 13**. Mahteme et al (2004) reported a significant difference in 2- and 5-year survival following CRS plus HIPEC compared with SC alone. Subanalysis of survival in patients treated with CRS plus HIPEC found 5-year survival of 37 and 14% in cases of macroscopically radical and incomplete resection, respectively. Similarly, Verwaal et al (2008) reported overall 2- and 5-year survival of 40 and 19% in patients treated with CRS plus HIPEC, compared with 22% and 10%, respectively, for patients receiving SC alone. The authors found survival to correlate significantly with the completeness of cytoreduction, with 5-year survival of 45%, 8%, and 0% in patients undergoing R1 (complete macroscopic tumour clearance), R2a (residual tumour nodules >2.5mm in thickness), and R2b (residual tumour nodules 42.5mm in thickness) resection, respectively.

**Figure 13.** Summary of meta-analysis results for 2-year survival following CRS plus HIPEC vs SC alone. The diamond represents the overall treatment effect, and squares are treatment effects for individual studies with 95% CI indicated by horizontal bars.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
<th>Odds ratio and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahteme et al</td>
<td>12.571</td>
<td>2.187</td>
<td>72.268</td>
<td>0.005</td>
<td></td>
<td>7.63</td>
</tr>
<tr>
<td>Verwaal et al</td>
<td>2.340</td>
<td>0.980</td>
<td>5.587</td>
<td>0.055</td>
<td></td>
<td>30.82</td>
</tr>
<tr>
<td>Elias et al</td>
<td>2.376</td>
<td>0.932</td>
<td>6.056</td>
<td>0.070</td>
<td></td>
<td>26.67</td>
</tr>
<tr>
<td>Franko et al</td>
<td>2.630</td>
<td>1.161</td>
<td>5.960</td>
<td>0.020</td>
<td></td>
<td>34.88</td>
</tr>
<tr>
<td>FEM</td>
<td>2.783</td>
<td>1.716</td>
<td>4.511</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elias et al (2009) reported 2- and 5-year survival and median survival of 81%, 51%, and 62.7 months, respectively, in 48 patients undergoing CRS plus HIPEC compared with 48 matched patients receiving SC alone (65%, 13% and 23.9 months, respectively). No data were available for survival according to extent of CPM or completeness of resection. Franko et al (2010) reported the median survival of 34.7 months in patients treated with CRS plus HIPEC, compared with 16.8 months.
with SC alone (\(P>0.001\)). Forest plots summarising pooled analysis of survival outcomes at 2 and 5 years with CRS plus HIPEC vs SC alone are shown in Figures 2 and 3. Heterogeneity analysis revealed no significant between-study inconsistencies (2-year data: Q-value 3.14; df (Q) 3; P-value 0.377; \(I^2\) 4.33; 5-year data: Q-value 2.66; df (Q) 3; P-value 0.488; \(I^2\) 0.00), and consequently estimates for OR and corresponding CI were derived using the FEM. Our meta-analysis demonstrated a significant improvement in 2-year survival with CRS plus HIPEC compared with SC alone (OR=2.78; 95% CI 1.72–4.51; \(P=0.001\); funnel plot analysis shown in Figure 13).

Similarly, meta-analysis of 5-year survival data from the four included studies revealed significantly enhanced survival at 5 years in patients treated with CRS plus HIPEC compared with SC alone (OR=4.07; 95% CI 2.17–7.64; \(P=0.001\); Figure 14).

**Figure 14.** Summary of meta-analysis results for 5-year survival following CRS plus HIPEC vs SC alone. The diamond represents the overall treatment effect, and squares are treatment effects for individual studies with 95% CI indicated by horizontal bars.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahteme et al</td>
<td>6.538</td>
<td>0.679</td>
<td>62.987</td>
<td>0.104</td>
<td>8.38</td>
</tr>
<tr>
<td>Verwaal et al</td>
<td>2.096</td>
<td>0.661</td>
<td>6.642</td>
<td>0.209</td>
<td>32.30</td>
</tr>
<tr>
<td>Elias et al</td>
<td>7.000</td>
<td>2.510</td>
<td>19.521</td>
<td>0.000</td>
<td>40.87</td>
</tr>
<tr>
<td>Franko et al</td>
<td>6.120</td>
<td>1.330</td>
<td>28.165</td>
<td>0.020</td>
<td>18.45</td>
</tr>
<tr>
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<td>2.387</td>
<td>8.860</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

**Morbidity, mortality, patient reported outcome measures**

Two of the four studies provided morbidity and mortality data (Mahteme et al, 2004; Verwaal et al, 2008). Mahteme et al (2004) reported overall treatment-associated morbidity and mortality of 72% and 0%, respectively. Complications attributed to treatment with CRS plus HIPEC in this study included severe postoperative pain (4/18, 22%), persistent nausea and vomiting (2/18, 11%), transient neutropenia (1/18, 5.5%), prolonged ileus (1/18, 5.5%), and postoperative bowel obstruction (5/18, 27.5%). Verwaal et al (2008) reported a mortality rate of 7% (4/54) in the CRS and HIPEC group in the only randomised study in this field. In all cases this was secondary to the development of postoperative complications that included abdominal sepsis in two cases. Complications in this study were reported according to the WHO criteria, with an overall complication rate of 7% in 54 patients undergoing CRS plus HIPEC. Specifically, the most common grade 3 toxicities reported were leukopenia (15%), heart failure (8%), haemorrhage (6%), and
catheter-related infections (6%). The most common grade 4 toxicities were intestinal fistulae (15%), haemorrhage (8%), and renal failure (6%). Massive pulmonary embolus occurred in 4%.

The remaining two studies included in this meta-analysis did not provide morbidity or mortality outcome data (Elias et al, 2009; Franko et al, 2010). Neither of the studies evaluated provided any published QOL/patient-reported outcome measures or health economic data for evaluation.

Authors’ conclusion

Although limited by between-study heterogeneity, the data support the assertion that in carefully selected patients, multimodal treatment of CPM with CRS plus HIPEC has a highly positive prognostic impact on medium- and long-term survival compared with SC alone. There is a paucity of comparative data available on morbidity, QOL, and HE.

WHSSC commentary

The review question was clearly stated and inclusion criteria were defined for participants, intervention and outcomes. Criteria for study design were specific focusing on survival, mortality and morbidity. Limiting the search to English-language studies identified in one database plus references raised the potential for publication and language biases and may have resulted in the omission of other relevant studies. Two reviewers were involved in some aspects of data extraction, which minimised reviewer error and bias. Study validity was not formally assessed using modified SIGN criteria although this has now been replaced by the GRADE system developed through the Cochrane Collaboration. The results from these studies and any synthesis are plausible. Data from RCTs and non-randomised studies were pooled using meta-analysis; pooling studies with different design is questionable. The limited search and evidence that was based on a small number of studies with different designs suggests that the authors’ conclusions should be interpreted with caution.

Randomised Controlled Trials (RCT)

One RCT was identified (Verwaal et al., 2003) which included an extension study to 8-year follow-up (Verwaal et al., 2008). In this study patients with histologically proven peritoneal metastases of colorectal origin or positive cytology of ascites who were diagnosed either at first presentation or at recurrence of CRC were recruited (n=105). Patients were >71 years and fit for major surgery (normal bone marrow indices and normal renal and liver function. Initially for the first year of the study, patients who had received 5-fluourouracil (FU) within 12 months were excluded before random assignment but a protocol amendment was made to allow these patients to be recruited.
Standard Treatment

Surgery was only performed in cases of symptoms of intestinal obstruction, and consisted of either bypass or stoma surgery. Often, this type of surgery had already been performed before referral for random assignment. Patients started chemotherapy immediately after random assignment or after recovery from surgery. Chemotherapy was given in the local setting, usually by the patients' own medical oncologist, and consisted of FU (intravenous [IV] push-dose of 400 mg/m²) and leucovorin (IV 80 mg/m²) on an outpatient basis (modified Laufman regimen). Treatment was given weekly for 26 weeks, or until progression, death, or unacceptable toxicity. Patients who had already been treated with FU within 12 months before random assignment were treated with irinotecan (350 mg/m²) at 3 weekly intervals for 6 months or until progression or intolerable toxicity.

Experimental Treatment

Cytoreductive surgery

All procedures were carried out in the Netherlands Cancer Institute. Laparotomy under general anesthesia was performed from xyphoid to pubis. After opening the abdomen, the presence of macroscopic tumour deposits was recorded in seven abdominal regions: pelvis and sigmoid; right lower abdomen; small bowel and mesentery; omentum and transverse colon; subhepatic space and stomach; right subphrenic space; and left subphrenic space. The maximal tumor size was recorded in each region as: none, less than 1 cm, 1 to 5 cm, or more than 5 cm.

The objective of cytoreduction was to leave no macroscopic tumor behind, or at least to have limited residual tumor (<2.5 mm in thickness). To achieve this, the stripping of the parietal peritoneum was carried out as described by Sugarbaker et al. Infiltrated viscera were resected if this was compatible with retaining function. Most often this concerned the rectum, parts of small bowel and colon, the gall bladder, parts of the stomach, and the spleen. The greater omentum was routinely removed. Reconstruction of gastrointestinal continuity was postponed until after the lavage, to prevent entrapment of tumour cells in suture lines. At completion of cytoreduction, the absence of residual tumour was recorded as R-1. If the largest residual tumour was smaller than 2.5 mm, it was regarded as an R-2a resection. In cases of residual tumour larger than 2.5 mm, cytoreductive surgery was scored as R-2b. The total length of the operation, and blood loss were also recorded.

Hyperthermic intraperitoneal chemotherapy (HIPEC).

To increase the volume of the abdominal cavity and to prevent spillage of lavage fluid, the skin of the laparotomy wound was pulled up against a retractor. A plastic sheet covered the laparotomy opening to reduce heat loss and to avoid drug spilling. A central aperture was made to allow manipulation to achieve optimal drug and heat distribution. The perfusion circuit consisted of a centrally placed inflow catheter, outflow catheters, placement in the pelvis below left and right diaphragm, a roller pump, and a heat exchanger. Temperature probes were attached to inflow and
outflow catheters. Perfusion was started with a minimum of 3 L of isotonic dialysis fluid, at 1 to 2 L/min, and an inflow temperature of 41°C to 42°C. As soon as the temperature in the abdomen was stable above 40°C, MMC was added to the perfusate at a dose of 17.5 mg/m² followed by 8.8 mg/m² every 30 minutes. The total dose was limited to 70 mg at maximum. If the core temperature exceeded 39°C, the inflow temperature was reduced.

After 90 minutes, the perfusion fluid was drained from the abdomen, and bowel continuity was restored. A temporary colostomy was made in most cases if the rectum was resected. A draining gastrostomy and transgastric jejunal feeding tube were inserted. The outflow catheters were used for postoperative drainage of the abdomen cavity.

Postoperative Care

Patients stayed in the intensive care unit for 3 days. In cases of abdominal sepsis (faecal flora in drain fluid, high fever, sepsis), a laparotomy was performed to correct bowel leakage at an early stage. Jejunal tube feeding was begun on day 1. Parenteral nutrition was given until jejunal feeding could cover all nutritional needs. Oral fluid and food intake was resumed as soon as the gastrostomy production dropped below 500 mL per 24 hours.

Adjuvant Chemotherapy

Systemic chemotherapy was intended to start after 6 weeks beyond cytoreduction followed by HIPEC, and before 3 months after cytoreduction followed by HIPEC. The regimens as described in the standard therapy arm were used.

Toxicity/Complications

Chemotherapy-related toxicity was recorded using the World Health Organisation (WHO) scale. All postoperative complications were noted, and were graded as toxicity according to the WHO scale.

Follow-Up

All patients were seen at the outpatient clinic once every 3 months for 2 years, and every 6 months thereafter. The follow-up consisted of physical examination and serum CEA every 3 months and an abdominal CT scan of the abdomen every 6 months, starting 3 months after randomization in the standard arm and 3 months after cytoreduction followed by HIPEC in the experimental arm.

Results

Between January 1998 and August 2001, 105 randomly assigned in this study—51 to standard therapy and 54 patients to experimental therapy. Two patients proved ineligible—one patient with pseudomyxoma peritonei in the standard arm and one
with peritoneal mesothelioma in the experimental arm. All patients, including the ineligible ones, were included in the intention-to-treat analysis.

The patient group included 58 men and 47 women, with a median age of 54 years (range, 28 to 70 years). Fifty-eight patients had PC at their primary presentation, and 47 patients had the disease at recurrence. The primary sites were appendix in 18 patients, colon in 75, and rectum in 12. The patient and tumour characteristics were well balanced within both arms, except for a non-significant over representation of males in the “HIPEC” arm (63% v 47%; \( P > .11 \)). Tumour size and differentiation grade were equally distributed in both arms. The majority of the patients (95.8% standard arm; 98.0% HIPEC arm) had large tumours (T3 and T4). All patients with small tumors (3.1%; T1 and T 2) were patients with PC at recurrence of CRC (Table 10).

Table 10. Patient Characteristics – Verwaal et al., 2003

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>%</th>
<th>No. of Patients</th>
<th>%</th>
<th>No. of Patients</th>
<th>%</th>
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<td>rectum</td>
<td>6</td>
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<td>—</td>
<td>1</td>
</tr>
<tr>
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<td>2.1</td>
<td>1</td>
<td>2.0</td>
<td>2</td>
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<tr>
<td>T3</td>
<td>17</td>
<td>35.4</td>
<td>19</td>
<td>38.8</td>
<td>36</td>
</tr>
<tr>
<td>T4</td>
<td>29</td>
<td>60.4</td>
<td>29</td>
<td>59.2</td>
<td>58</td>
</tr>
</tbody>
</table>

*Data from four patients are missing.
†Data of eight patients are not available.

**Standard Arm**

Seven patients never started systemic chemotherapy: five patients withdrew their consent; two patients had severe progressive disease before they could start, and deteriorated rapidly. Thirty-eight patients started with FU-leucovorin, of whom 21 received treatment for at least 5.4 months (median, 5.8 months; range, 5.4 to 6.7); 12 stopped because of progression of disease; two stopped because of toxicity; and three were still on treatment. Six patients started with irinotecan, of whom two completed treatment.
Experimental Arm

Five patients did not undergo cytoreduction followed by HIPEC treatment. While waiting for surgery, one died due to rapid tumour progression; two patients developed lung and liver metastases, for which they were treated with palliative chemotherapy; and in one patient, a primary lung cancer was detected shortly after randomisation. This patient died shortly after randomisation. One patient withdrew consent. The median time between randomisation and surgery was 6 weeks (range, 6 days to 14 weeks). The median hospital stay of the 49 patients operated on was 29 days (range, 6 to 166 days). The median duration of the cytoreduction and HIPEC was 485 minutes (range, 315 to 765 minutes), while the median blood loss was 3.9 L (range, 0.5 to 30.0 L; for seven patients, data were not available). Of the seven possible affected regions, six or seven were involved in 16 patients. Those patients had a median operation time of 585 minutes (range, 440 to 765 minutes) and a median blood loss of 6.0 L (range, 3.5 to 30.0 L). In two patients, no macroscopic tumour was found at all, and peritoneal metastases had been resected at a previous laparotomy. Both received HIPEC without cytoreduction. The median hospital admission duration was 23 days (range, 13 to 90 days) for zero to five affected regions, and 38 days (range, 6 to 166 days) for six to seven regions.

An average of 1.8 visceral resections were performed per patient. Most often, parts of small bowel (45 patients) and rectum (25 patients) were resected. Twenty-four patients needed a colostomy. The median number of bowel anastomoses was two (range, zero to seven anastomoses). In 18 patients, no macroscopic residual disease was left behind (R-1); in 21, the residual deposits were smaller than 2.5 mm (R-2a); and in 10 cases, residual deposits were ≥2.5 mm (R-2b). Grade 3 and 4 toxicity, as well as complications, are shown in Table 11.

Table 11. Major Toxicity and Complications of 48 Patients With Peritoneal Carcinomatosis Treated by Cytoreduction Followed by HIPEC

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia (paros)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolus (within 3 months after surgery)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal obstruction</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Anuria (acute tubular necrosis)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>GI fistula</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Catheter infections</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Psychological disorders</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; GI, gastrointestinal.
The surgical complications are recorded as toxicity, as described in the WHO criteria. Only bone marrow toxicity (14% grade 3, and 5% grade 4) is definitely attributable to MMC. The nadir was between 10 and 12 days. All other toxicity is most likely due to surgery or to an interaction between MMC and major surgery. The most important complications were small bowel leakage and abdominal sepsis. Four patients (8%) died as a result of the treatment. Two patients (4%) died of abdominal sepsis within 30 days after cytoreduction followed by HIPEC. Two other patients (4%) never recovered and died of a complicated postoperative course.

Fourteen patients never started adjuvant chemotherapy after cytoreduction followed by HIPEC. This was because of early progression (eight patients) or refusal (three patients). All 33 patients who started chemotherapy received FU-leucovorin. Nineteen completed 6 months of therapy, four stopped early because of disease progression, two stopped because of toxicity, and one withdrew consent. At the time of closing the database, seven patients were still receiving the treatment.

Survival

One patient was lost during follow-up after 7 months, while the follow-up was complete for all other patients. After a median follow-up of 21.6 months, 20 patients were still alive in the standard treatment group, compared with 30 patients in the HIPEC group. Cytoreduction followed by HIPEC significantly reduced the risk of dying (hazard ratio, 0.55; 95% CI, 0.32 to 0.95; log-rank \( P = 0.032 \)). Median survival in the standard arm was 12.6 months, compared with 22.4 months in the HIPEC arm (\( P = 0.032 \); Figure 15).

Exploratory subgroup analysis did not reveal any particular subgroup in which the effect of cytoreduction followed by HIPEC was better or worse compared with standard treatment (Figure 16). When the data of the patients who underwent cytoreduction followed by HIPEC were further analysed, they showed that patients with six to seven regions still had a very poor survival (median, 5.4 months) compared with those with zero to five regions involved (median, >29 months; Figure 17 ; \( P < 0.0001 \)). The success of the surgical procedure also had prognostic value. After complete resection (R-1), only one of 18 patients died. Fourteen of the 21 patients with limited residual disease (R-1a) died, compared with seven of the 10 patients with extensive residual disease (R-2b) (\( P <0 .0001 \)). The median times to death in the latter two groups were 20 and 5 months, respectively (Figure 18).
Figure 15. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

Figure 16. Explorative subgroup analysis on survival of all 105 patients randomized. This Forest plot shows the hazard ratio (odds of death) for various subgroups of patients. The size of the squares represent the number of patients, the horizontal lines through the squares indicate the 99% CIs. The diamond indicating the overall result corresponds with the 95% CI. HIPEC, hyperthermic intraperitoneal chemotherapy.
Figure 17. Kaplan-Meier survival curve of 49 patients with peritoneal Carcinomatosis (PC) treated by cytoreduction followed by hyperthermic intraperitoneal chemotherapy, comparing the number of regions affected with PC.

Figure 18. Kaplan-Meier survival curve of 49 patients with peritoneal carcinomatosis treated by cytoreduction followed by HIPEC, comparing the number of regions with residual tumour.
Authors’ conclusion

Cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. However, patients with involvement of six or more regions of the abdominal cavity, or grossly incomplete cytoreduction, had still a grave prognosis.

WHSSC commentary

This is a key study and the only RCT undertaken to date. The randomisation and concealment allocation to SC or the experimental arm was appropriate. The end points studies included survival, mortality and morbidity. The results of this study are plausible. However, there was a significant attrition rate in both arms of the study (5 in the SC arm and 7 in the CRS plus HIPEC arm) although these data are accounted for as part of the intention to treat analysis. The change in protocol after 12-months recruitment may be a significant confounder which is not addressed in the discussion section of the study. Complete or nearly complete resection seems to be a prerequisite for a favourable outcome. The other limitations of the study are noted by the authors, namely that the study used a moderately dosed regimen of FU-leucovorin. More aggressive schedules of combination chemotherapy have been introduced in advanced colorectal cancer, which are associated with a greater survival benefit compared to the chemotherapy regimen used in this study.

In the extension study by Verwaal et al., 2008, these patients were followed-up until 2007. Progression-free and disease-specific survival were analysed using the Kaplan Meyer test and compared using the log rank method. The long-term results were studied in more detail to evaluate efficacy and toxicity. At the time of this update, the median follow-up was almost 8 years (range 72– 115 months). In the standard arm, 4 patients were still alive, 2 with and 2 without disease; in the “HIPEC” arm, 5 patients were still alive, 2 with and 3 without disease. The median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm (P = 0.020). The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm (P = 0.028). The 5-year survival was 45% for those patients in whom a R1 resection was achieved.

Authors’ conclusion

With 90% of all events having taken place up to this time, this randomized trial shows that cytoreduction followed by HIPEC does significantly add survival time to patients affected by peritoneal carcinomatosis of colorectal origin. For a selected group, there is a possibility of long-term survival.
The extension study re-enforced the association between complete resection and longer term survival. Clearly at 8-years follow-up any survival benefit of CRS plus HIPEC vs. SC has been eroded with similar numbers of survivors in each treatment arm.

**Comparative Case Series Studies**

Three comparative case series studies were identified (Mahteme et al., 2004; Elias et al., 2009; Franko et al., 2010) in n=151 patients.

**In Mahteme et al., 2004** the effects of debulking surgery and i.p. chemotherapy with respect to survival were assessed in 18 patients and compared the results with matched control patients treated by intravenous (i.v.) chemotherapy.

**Patient selection**

The inclusion criteria were primary colorectal adenocarcinoma (colon 16, rectal 2), with local or peritoneal tumour deposits either resectable or suitable for debulking surgery, and without hepatic or other extra abdominal tumour growth as judged from laparotomy, chest X-ray and ultrasonography/CT scan, age ≤75 years and American Society of Anesthesiologists (ASA) classification grades 1–2. Informed consent was obtained from each patient. The diagnosis of the primary tumour and the metastases were verified histopathologically. One patient was not treated according to the protocol because of extensive irresectable peritoneal tumour growth. The remaining 17 patients were treated by either total macroscopic removal (11) or debulking (6) of the metastases followed by i.p. chemotherapy. In four patients, the diagnosis of local or peritoneal spread was carried out concomitant with the diagnosis of the primary tumour, and in the remaining 14 patients there was an interval of mean 19 (range 1–52) months between the diagnosis of the primary tumour and the local/peritoneal recurrence. A system for classification of local/peritoneal spread was set up based on which all patients could be classified: (a) predominant peritoneal growth7smaller local deposits; (b) predominant local growth7smaller peritoneal deposits; and (c) predominant abdominal wall growth7smaller local or peritoneal deposits. Two patients were classified in group a, six in group b and 10 in group c.

**Results**

**Treatment effect**

The median number of i.p. chemotherapy courses was 3 (1–8). Four patients had pain during or immediately after the i.p. infusion; however, none of the patients
terminated the planned treatment because of infusion-related pain. Leakage from the drain site was noted in one patient. Two patients suffered repetitively from nausea and vomiting during the i.p. treatment period, and transient neutropenia was noted in one patient. Of the patients, 13 terminated the planned treatment prematurely, seven of them because of catheter-related problems (local catheter infection (1), improper position (1), obstruction (5)), ileus 1, liver metastases 1, decline in general status 1 and two patients refused further treatment. Single photon emission computed tomography studies showed a median abdominal cavity distribution volume of 2896 ml (range 32–11 557). In one patient, treatment was withdrawn after SPECT because of the lack of widespread distribution in abdominal cavity. In five patients the PORT-A-CATH was reoperated. There was no mortality related to surgery or to the i.p. treatment. In one patient who was not treated with cytoreductive surgery, no i.p. chemotherapy was administered.

**Survival**

The median survival in i.p. patients was 32 months (95% confidence interval (CI ) 22.2–62.6 months), whereas in the i.v. control group it was 14 months (95% CI 5.6–24.9 months), (P=0.01, **Figure 19**). A 2 and 5 years survival in i.p. patients were 60 and 28%, whereas corresponding values in the i.v. control group were 10 and 5%. In all, 11 patients who were considered macroscopically tumour free after the tumour reduction procedure had a longer survival (34.5 months, 95% CI 28.7–75.7) than those who did not undergo macroscopically radical surgery (10 months, 95% CI -15.7 to 70.0), (P=0.02, **Figure 20**). Five patients in whom radical surgery could be performed are still alive (median 8.3 years, range 6.8–9.1) after surgery. One patient who underwent radical surgery survived only 4 months. One patient who was considered not to be macroscopically tumour free after the tumour reduction procedure is still alive and has survived 10.8 years. In total, 10 patients in whom radical surgery was not performed survived median 13 months (range 3 months–10.8 years).

**Figure 19. Cumulative proportion surviving (Kaplan–Meier), Mahteme et al., 2004**
Authors’ conclusion

These results indicate that patients with peritoneal metastases and/or locally advanced cancers but without distant metastases may benefit from cytoreductive surgery combined with i.p. chemotherapy.

WHSSC commentary

This series is not a prospective-randomised study, and a selection of patients may have influenced the results. However, in an attempt to compare the loco-regional treatment to standard i.v. chemotherapy, we used historical controls. The two combinations (MFL and FLv) of chemotherapy, both based on biochemical modulation of 5-FU, were equally effective with respect to survival and response rates in a previous clinical trial.

It is therefore reasonable to consider these two combinations as equal at the time the study was undertaken. However, the more recently developed combination regimen are even more effective than those used in the Nordic chemotherapy trials.

The relative importance of the i.p. chemotherapy cannot be properly assessed in the present study.
In Elias et al. 2009, 48 patients with gross PC from colorectal adenocarcinoma who had undergone cytoreductive surgery plus HIPEC at the Gustave Roussy Institute (Villejuif, France) from January 1998 to December 2003 were prospectively included.

**Patient Selection**

These patients were selected preoperatively according to the following criteria: (1) no huge and symptomatic PC, (2) no extra-abdominal malignancy, (3) a good general status and younger than 66 years old, and (4) no disease progression after 2 to 3 months of neoadjuvant chemotherapy. To classify the extension of the PC, the abdominopelvic cavity was divided into five regions that included the four abdominal quadrants plus the pelvis. Before CRS, the distribution of PC was noted: one or two regions invaded defined limited PC, whereas three or more regions defined extended PC. CRS was always complete, with no residual peritoneal disease exceeding 1 mm in diameter. Peritonectomy procedures have been described in previous studies.

HIPEC was administered intraperitoneally with oxaliplatin 460 mg/m² in 2 L/m² of dextrose at a temperature of 43°C (two in-flow drains at 45°C and two out-flow drains at > 42°C) over 30 minutes after attaining the minimal temperature of 42°C throughout the abdominal cavity (5 to 10 minutes were required to warm the liquid from 37°C to 42°C), with a flow rate of 2 L/min. Before the beginning of HIPEC, and during CRS, patients had received intravenous fluorouracil 400 mg/m² and leucovorin 20 mg/m² to potentiate oxaliplatin activity. Because fluorouracil cannot be mixed with oxaliplatin inside the peritoneal cavity (because of pH incompatibility), it was administered intravenously to bathe the tumour and healthy tissue before HIPEC.

**CRS plus HIPEC plus SC Group**

All patients with gross PC from colorectal adenocarcinoma who had undergone CRS plus HIPEC at the Gustave Roussy Institute (Villejuif, France) from January 1998 to December 2003 were prospectively included. These patients were selected preoperatively according to the following criteria: (1) no huge and symptomatic PC, (2) no extra-abdominal malignancy, (3) a good general status and younger than 66 years old, and (4) no disease progression after 2 to 3 months of neoadjuvant chemotherapy. To classify the extension of the PC, the abdominopelvic cavity was divided into five regions that included the four abdominal quadrants plus the pelvis. Before CRS, the distribution of PC was noted: one or two regions invaded defined limited PC, whereas three or more regions defined extended PC. CRS was always complete, with no residual peritoneal disease exceeding 1 mm in diameter. Peritonectomy procedures have been described in previous studies. HIPEC was administered intraperitoneally with oxaliplatin 460 mg/m² in 2 L/m² of dextrose at a temperature of 43°C (two in-flow drains at 45°C and two out-flow drains at >42°C) over 30 minutes after attaining the minimal temperature of 42°C throughout the abdominal cavity (5 to 10 minutes were required to warm the liquid from 37°C to
42°C), with a flow rate of 2 L/min. Before the beginning of HIPEC, and during CRS, patients had received intravenous fluorouracil 400 mg/m$^2$ and leucovorin 20 mg/m$^2$ to potentiate oxaliplatin activity. Because fluorouracil cannot be mixed with oxaliplatin inside the peritoneal cavity (because of pH incompatibility), it was administered intravenously to bathe the tumour and healthy tissue before HIPEC.

**Standard Group**

The authors performed a retrospective study on highly selected patients with colorectal PC treated with palliative chemotherapy during the same period in five French comprehensive anticancer centers. This control group of comparable patients had received standard chemotherapy combined or not with palliative surgery. These patients had not benefited from HIPEC because the technique was unavailable in these five centres and because patients could not be referred to the reference centre because of its limited treatment capacity. Patients were highly selected to ensure comparability with the CRS plus HIPEC plus SC group. The selection process was divided into two steps. During the first step, surgeon investigators from each anticancer centre selected from their records all patients with colorectal PC diagnosed between January 1998 and December 2003 who had been treated with palliative chemotherapy and who met eligibility criteria.

Eligibility criteria included those defined as good prognostic factors for HIPEC in the literature:1 (1) a good general status (WHO performance status of 1 to 2), (2) <65 years, (3) no extra-abdominal extension, (4) no evidence of bowel obstruction, (5) no tumour larger than 2 cm at computed tomography, and (6) no rapid progression of PC under SC. During the second step, the principal investigator (D.E.) double-checked the medical records of the potentially eligible patients provided by the centers by recontacting the investigators to ensure that the eligibility criteria had been applied homogeneously. During double-checking, the investigator was blinded to the detailed characteristics of the patients in the CRS plus HIPEC plus SC group.
Table 12. Patient Characteristics at Diagnosis of Peritoneal Carcinomatosis, Elias et al., 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIPEC (n = 48)</th>
<th>Standard Treatment (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, %</td>
<td>36</td>
<td>34</td>
<td>.8</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>46</td>
<td>51</td>
<td>.01</td>
</tr>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>40</td>
<td>41</td>
<td>.9</td>
</tr>
<tr>
<td>Rectum</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Initial pT staging, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1, T2</td>
<td>0</td>
<td>3</td>
<td>.08</td>
</tr>
<tr>
<td>T3</td>
<td>23</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lymph node status, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>34</td>
<td>31</td>
<td>.07</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tumor differentiation, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>37</td>
<td>29</td>
<td>.02</td>
</tr>
<tr>
<td>Poor</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Extension of PC, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>27</td>
<td>26</td>
<td>.07</td>
</tr>
<tr>
<td>Extended</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CEA rate, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>33</td>
<td>40</td>
<td>.1</td>
</tr>
<tr>
<td>≥ 30</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total No. of lines of chemotherapy</td>
<td>102</td>
<td>110</td>
<td>.52</td>
</tr>
</tbody>
</table>

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; PC, peritoneal carcinomatosis; CEA, carcinoembryonic antigen.

Comparison of the Two Groups

Patient characteristics are detailed in Table 12. All characteristics were comparable, except age and tumour differentiation. Patients in the CRS plus HIPEC plus SC group were significantly younger. The Cox regression model applied to our data showed that the survival benefit was not sensitive to age nor to tumour differentiation. There was no difference in SC, either in the type of agents used or in the number of lines administered in each group (102 v 110; P =0 .52). In the CRS plus HIPEC plus SC group, all patients had received neoadjuvant therapy; intraperitoneal chemotherapy consisted of oxaliplatin for 30 patients and oxaliplatin combined with irinotecan for the remaining 18 patients. In the standard group, the 48 patients had received a first line of chemotherapy, 33 patients had received a second line, 17 patients had received a third line, and 12 patients had received a fourth line (Tables 13 and 14), resulting in a mean of 2.3 lines of chemotherapy per patient.
Survival Analysis

Median follow-up was 95.7 months in the standard group, whereas it was 63 months in the CRS plus HIPEC plus SC group. This difference is at least partly because the study of survival was started at different times: it was the date of first-line systemic chemotherapy in the control group, but the date of HIPEC in the CRS plus HIPEC plus SC group (even though all patients in this group had received SC). Two year overall survival was 65% (95% CI, 55% to 74%) for the standard group versus 81% (95% CI, 68% to 90%) for the CRS plus HIPEC plus SC group. Five-year overall survival was 13% (95% CI, 6% to 26%) for the standard group versus 51% (95% CI, 36% to 65%) for the CRS plus HIPEC plus SC group. Kaplan-Meier curves are shown in Figure 21: the survival rate of patients in the CR plus HIPEC vs. SC group was significantly ($P < 0.05$) higher than that of the standard group. Median survival was 23.9 months in the standard group versus 62.7 months in the CRS plus HIPEC plus SC group ($P < 0.05$, two-sided log-rank test).

Table 13. Details of the Different Chemotherapy Regimens Received by the Standard Group, Elias et al., 2009
Fig 21. Overall survival of group receiving cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic treatment versus those receiving standard treatment, Elias et al., 2009

Table 14. Systemic Chemotherapy Lines, Elias et al., 2009

<table>
<thead>
<tr>
<th>Type of CT</th>
<th>No. of Courses</th>
<th>CRS + HIPEC + SC</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modern CT agents</td>
<td>81</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin combined with other agents</td>
<td>48</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Irinotecan alone or combined with other agents</td>
<td>33</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Other CT agents</td>
<td>20</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil alone or combined with other agents</td>
<td>18</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Other (paclitaxel, carboplatin, and so on)</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CT, chemotherapy; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; SC, systemic chemotherapy.

Authors’ conclusion

Patients with isolated, resectable PC achieve a median survival of 24 months with modern chemotherapies, but only surgical cytoreduction plus HIPEC is able to prolong median survival to roughly 63 months, with a 5-year survival rate of 51%.
WHSSC commentary

The data presents comparative case series data for CRS plus HIPEC vs. SC. The combination of first second and third line chemotherapy in the standard care arms makes treatment comparison difficult to interpret but is reflective of the management of these patients in a real life context. The survival effect at 2-years is consistent with that produced in the Verwaal et al., 2003 but the lack of randomisation and concealment may bias the study.

In Franko et al., 2010, 67 consecutive patients underwent CRS combined with HIPEC and systemic chemotherapy for metastatic colorectal cancer. The control group was selected by a review of the institutional multihospital cancer registry and consisted of 38 patients. Control group inclusion criteria were 1) asymptomatic peritoneal carcinomatosis of colorectal origin; 2) aggressive systemic chemotherapy; and 3) primary tumour removed, but did not undergo CRS plus HIPEC. Control group exclusion criteria included 1) poor performance status, 2) intent for supportive care only, and 3) unresectable carcinomatosis volume as judged by computed tomography (CT) scan review. The diagnosis of peritoneal carcinomatosis in the control group was verified by a surgical procedure or by the development of obvious evidence of carcinomatosis on CT scan. Presence of limited liver involvement (superficial lesions only) was allowed in both groups. Demographics, tumour characteristics (grade, TNM stage, and site of original tumour), chemotherapy treatment, and survival outcome were analysed.

Results

There was no statistical difference between the groups in distribution of sex, tumour grade, site of origin (colon vs rectum), and T and N classification of the original tumour. However, the control group was older (mean 59 years in the control group vs mean 51 years in the hyperthermic intraperitoneal chemoperfusion group; P<.001), had a higher proportion of patients who were diagnosed with carcinomatosis at their initial presentation (76% vs 42%; P<.001), and had a higher proportion of patients with liver lesion (35% vs. 15%; P=.014).

All patients received systemic chemotherapy. There were no differences between the 2 groups in administration of 5-fluorouracil and irinotecan, but the control group was less likely to receive oxaliplatin (47% vs. 78%; P=0.001) and biological agents (bevacizumab and/or cetuximab, 18% vs 59%; P<.0001). Six patients in the CRS plus HIPEC group received a suboptimal debulking (R2), but remained included in the study.

Median survival measured from the diagnosis of peritoneal disease was longer with cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion
(34.7 months vs 16.8 months; P<.001; **Figure 22**). Besides CRS plus HIPEC, only chemotherapy with biological agents and absence of liver metastasis were associated with survival advantage in the univariate testing (**Table 15**). Sex, tumour grade, site of primary tumour origin (colonic vs rectal), and presence of carcinomatosis at initial cancer diagnosis (stage I-III vs stage IV/carcinomatosis) were not associated with survival.

**Figure 22.** Kaplan-Meier estimator curves comparing the group treated with CRS plus HIPEC versus the control group are shown. Chemo indicates chemotherapy, Franko *et al.*, 2010.

Multivariate Cox proportional hazards modelling was performed on all patients with available data. Tumour grade was the only variable that violated the proportional hazard assumption. On detailed analysis, there is some evidence that tumour grade affects survival, particularly at early times. Conversely, tumour grade is not a confounder, because it is not associated with CRS combined HIPEC treatment.
Therefore, 3 Cox proportional hazard regression models were developed, where the latter 2 represent sensitivity analysis and point to the robustness of the results. There were 91 cases available for the first model, which included significant predictor variables from univariate testing (Table 15). Tumour grade lacked the predefined

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median Survival, mo</th>
<th>Statistical Significance$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>16.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CS-HIPEC</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>26.3</td>
<td>.777</td>
</tr>
<tr>
<td>Men</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and 2</td>
<td>27.5</td>
<td>.322</td>
</tr>
<tr>
<td>3</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td><strong>Site of origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>26.9</td>
<td>.109</td>
</tr>
<tr>
<td>Rectum</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td><strong>Initial presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary tumor with carcinomatosis</td>
<td>26.3</td>
<td>.825</td>
</tr>
<tr>
<td>Stage I-III primary tumor</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td><strong>Liver lesion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>30.3</td>
<td>.001</td>
</tr>
<tr>
<td>Present</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td><strong>Oxaliplatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26.3</td>
<td>.323</td>
</tr>
<tr>
<td>Yes</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27.5</td>
<td>.946</td>
</tr>
<tr>
<td>Yes</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td><strong>Biological agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19.7</td>
<td>.020</td>
</tr>
<tr>
<td>Yes</td>
<td>30.3</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Factors found to be associated with survival were CS-HIPEC, the presence of a liver lesion, and systemic chemotherapy with a biologic agent.
entry P value and consequently was not included in this model. Delivery of CRS plus HIPEC was a significant predictor of survival after adjusting for all other variables. Presence of liver metastasis was a negative significant predictor of survival, and its effect size was comparable to that of CRS plus HIPEC.

Table 16. Multivariate Cox Regression Model for Survival Since Diagnosis of Carcinomatosis Adjusted for Baseline Predictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistical Significance</th>
<th>HR</th>
<th>95% HR CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (referent: control)</td>
<td>.0273</td>
<td>0.421</td>
<td>0.195-0.907</td>
</tr>
<tr>
<td>Site of origin (referent: colon)</td>
<td>.0588</td>
<td>2.237</td>
<td>0.971-5.154</td>
</tr>
<tr>
<td>Liver lesion (referent: colon)</td>
<td>.0366</td>
<td>2.133</td>
<td>1.049-4.341</td>
</tr>
<tr>
<td>Biological agents</td>
<td>.4672</td>
<td>0.776</td>
<td>0.392-1.586</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>.8624</td>
<td>0.945</td>
<td>0.496-1.798</td>
</tr>
<tr>
<td>Age</td>
<td>.6825</td>
<td>1.008</td>
<td>0.981-1.035</td>
</tr>
<tr>
<td>Carcinomatosis at initial presentation</td>
<td>.1379</td>
<td>0.607</td>
<td>0.314-1.174</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence limits.

* A total of 91 cases were available for analysis; overall P = .002.

** Group: group treated with systemic chemotherapy alone as the referent versus the group treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion (CS-HIPEC). The risk of death was found to be significantly lowered among patients treated with CS-HIPEC (HR, 0.421). A HR > 1 indicates an increased risk of death.

Table 17. Multivariate Cox Regression Model Stratified Based on Tumour Grade

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistical Significance</th>
<th>HR</th>
<th>95% HR CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (referent: control)</td>
<td>.2426</td>
<td>0.598</td>
<td>0.253-1.416</td>
</tr>
<tr>
<td>Site of origin (referent: colon)</td>
<td>.1394</td>
<td>2.247</td>
<td>0.768-6.572</td>
</tr>
<tr>
<td>Liver lesion</td>
<td>.0030</td>
<td>3.575</td>
<td>1.540-8.298</td>
</tr>
<tr>
<td>Biological agents</td>
<td>.1620</td>
<td>0.562</td>
<td>0.284-1.235</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>.9502</td>
<td>1.022</td>
<td>0.512-2.041</td>
</tr>
<tr>
<td>Age</td>
<td>.5902</td>
<td>1.069</td>
<td>0.977-1.041</td>
</tr>
<tr>
<td>Carcinomatosis at initial presentation</td>
<td>.2940</td>
<td>0.687</td>
<td>0.341-1.385</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence limits.

* A total of 75 cases were available for analysis; overall P = .002.

** Group: group treated with systemic chemotherapy alone as referent versus group treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion (CS-HIPEC). The risk of death was not found to be significantly altered among patients treated with CS-HIPEC (P = .242).
Carcinomatosis from rectal primary tumours portends a substantially worse prognosis than that from a colon primary tumour. Age and the presence of carcinomatosis at initial presentation of cancer were not predictive of survival. Moreover, chemotherapy with oxaliplatin or a biological agent was also not a predictor of survival. We attempted to include tumour grade as a variable in the analysis.

Because tumour grade did not follow the proportional hazard assumption, the second model was stratified on tumour grade. There were 75 cases with data available for this analysis: 51 patients in stratum 1 (grade I-II) and 24 patients in stratum 2 (grade III). Each group has a distinct baseline hazard function, but common values for the coefficients.

The relative effect of each predictor is assumed the same across strata. The presence of liver lesion(s) was the only significant predictor of survival in the model (Table 16). To further investigate the effect of missing values for tumour grade, we developed a third model. This model included 91 cases, and contained all variables from the first model plus a dummy variable for whether grade was reported. There was no substantial change of covariate values, and the regression coefficient for the dummy variable was not statistically significant (Table 17).

Authors’ conclusions

The authors concluded that 1) contemporary chemotherapy is associated with prolonged survival among patients with carcinomatosis as compared with historical controls, and 2) addition of CRS plus HIPEC to modern chemotherapy regimens may significantly prolong survival. Cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion and systemic chemotherapy are not competitive therapies, and they both have a role in a multidisciplinary approach to patients with carcinomatosis.

WHSSC commentary

The study was designed as a case control comparative study. Although there were no differences between the 2 groups in administration of 5-fluorouracil and irinotecan, the control group was less likely to receive oxaliplatin (47% vs 78%; P=0.001) and biological agents (bevacizumab and/or cetuximab, 18% vs 59%; P<.0001). Six patients in the CRS plus HIPEC group received a suboptimal debulking (R2), but remained included in the study. Both these issues may confound the end result but it is difficult to predict the impact either of these issues would have of overestimating (or underestimating) effect size in the control or CRS plus HIPEC.
The study suffers from a lack of randomisation or concealment allocation which may bias the result.

Case Series

The literature search identified 17 case series studies (Witkamp et al., 2001; Glehen et al., 2004a; Verwaal et al., 2005; Elias et al., 2009; Elias et al., 2010; Franko et al., 2010; Quenet et al., 2011; Vaira et al., 2010; Kuijpers et al., 2013; Robella et al., 2013; Hompes et al., 2013; Teo et al., 2013; Weber et al., 2013; Cashin et al., 2014; Kuijpers et al., 2014 and Rivard et al., 2014) in 3,952 patients.

Key Case Series

In Glehen et al., 2004a, a retrospective multicenter study was performed to evaluate the international experience with this combined treatment and to identify the principal prognostic indicators. All patients had cytoreductive surgery and perioperative intraperitoneal chemotherapy (intraperitoneal chemohyperthermia and/or immediate postoperative intraperitoneal chemotherapy). PC from appendiceal origin was excluded.

Results

The study included 506 patients from 28 institutions operated between May 1987 and December 2002. Their median age was 51 years. The median follow-up was 53 months. The morbidity and mortality rates were 22.9% and 4%, respectively. The overall median survival was 19.2 months. Patients in whom cytoreductive surgery was complete had a median survival of 32.4 months, compared with 8.4 months for patients in whom complete cytoreductive surgery was not possible (P < .001). Positive independent prognostic indicators by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of PC, age less than 65 years, and use of adjuvant chemotherapy. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were negative independent prognostic indicators.

Authors’ conclusions

The therapeutic approach combining cytoreductive surgery with perioperative intraperitoneal chemotherapy achieved long-term survival in a selected group of patients with PC from colorectal origin with acceptable morbidity and mortality. The complete cytoreductive surgery was the most important prognostic indicator.
WHSSC Commentary

This is one of the largest case series studies identified. Appendiceal patients were excluded from the analysis to avoid confounding. The duration of follow-up was appropriate to review findings on survival, mortality and morbidity. The study provided useful data on patient selection and prognostic indicators.

Safety

Two systematic reviews (Tan et al., 2014; Mirnezami et al., 2014), one RCT (Verwaal et al., 2003), one comparative case series (Mahteme et al., 2004) and two non-comparative case series (Piso et al., 2009; Baratti et al., 2014 N=138) reported specifically of safety outcomes and adverse events.

Two of the four studies in Mirnezami et al., 2014 provided morbidity and mortality data (Mahteme et al., 2004; Verwaal et al., 2008). Mahteme et al (2004) reported overall treatment-associated morbidity and mortality of 72% and 0%, respectively. Complications attributed to treatment with CRS plus HIPEC in this study included severe postoperative pain (4/18, 22%), persistent nausea and vomiting (2/18, 11%), transient neutropenia (1/18, 5.5%), prolonged ileus (1/18, 5.5%), and postoperative bowel obstruction (5/18, 27.5%). Verwaal et al (2008) reported a mortality rate of 7% (4/54) in the CRS and HIPEC group in the only randomised study in this field. In all cases this was secondary to the development of postoperative complications that included abdominal sepsis in two cases. Complications in this study were reported according to the WHO criteria, with an overall complication rate of 7% in 54 patients undergoing CRS plus HIPEC. Specifically, the most common grade 3 toxicities reported were leukopenia (15%), heart failure (8%), haemorrhage (6%), and catheter-related infections (6%). The most common grade 4 toxicities were intestinal fistulae (15%), haemorrhage (8%), and renal failure (6%). Massive pulmonary embolus occurred in 4%.

In Piso et al., 2009, between 2005 and 2008, 204 patients underwent CRS and HIPEC at a tertiary referral centre. Of these, 37 procedures (male/female 24/13, median age 55 years) included gastric resections. The clinical data of all patients were introduced into a database and analysed with respect to the morbidity associated with the gastric resections.

Results

Of all patients included, 16 had pseudomyxoma peritonei, 11 gastric carcinoma, 4 ovarian carcinoma, 3 malignant peritoneal mesothelioma, and 3 colon carcinoma. Twenty-seven patients had previous surgery (n = 22) and/or systemic chemotherapy
Fifteen total gastrectomies, 3 subtotal gastrectomies, 12 distal gastrectomies, and 7 gastric wedge resections were performed during CRS. The overall postoperative morbidity was 45%; main surgical complications were pancreatitis (n = 6), abdominal abscess (n = 4), bile leakage (n = 2), and digestive fistula (leakage of ileorectostomy and small bowel perforation) (n = 2). However, no complications occurred at the site of the oesophageal anastomosis (n = 15), gastric anastomosis (n = 15) or gastric suture (n = 7). No patient died postoperatively during the hospitalisation period.

Authors’ conclusions

CRS in combination with HIPEC is associated with high postoperative morbidity; however, anastomosis following total or subtotal gastrectomy is safe in experienced centers. No leakages related to gastric resections occurred in this high-risk patient group.

WHSSC Comment

This is an observational, selective study in small numbers of patients looking at CRS plus HIPEC plus gastric resection in a high-risk, heterogeneous population including PMP, and a large variety of tumour seeding leading to PM.

In Baratti et al., 2014, two prospective databases were reviewed. Major complications were defined as grade 3 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The extent of peritoneal involvement was scored by the use of the Peritoneal Cancer Index. Peritoneectomy procedures and multivisceral resections were used to remove all macroscopic tumour, and mitomycin-C plus cisplatin-based HIPEC was used to control microscopic residual disease based on 101 patient records.

Results

Mortality and major morbidity were 3.0%, and 23.8%. Median follow-up was 44.9 months (95% CI, 24.1-65.7). Five-year disease-specific survival was 14.3% for patients who experienced major complications and 52.3% for those who did not (p = 0.001). Five-year overall survival was 11.7% for patients who experienced major complications, and 58.8% for those who did not (p = 0.003). At multivariate analysis, major morbidity correlated to both worse overall and disease-specific survival, along with a Peritoneal Cancer Index >19, and suboptimal cytoreduction. Poor performance status correlated only to worse disease-specific survival, and liver metastases correlated to worse overall survival. Longer operative time (OR, 4.1; 95% CI, 1.3-12.6; p = 0.01) and Peritoneal Cancer Index >19 (OR, 2.6; 95% CI, 1.1-6.0; p = 0.02) were independent risk factors for major morbidity.
Authors’ conclusion

The prevention of major complications, by refining surgical technique and patient selection, is crucial because it affects oncologic outcome.

WHSSC Commentary

This study is limited by its observational design although the results are consistent with the available data from systematic review and meta-analysis.

Recurrance rates

The literature search identified 4 case series studies (Verwaal et al., 2004; Cashin et al., 2012; Sardi et al., 2013; Baraam et al., 2014) reporting recurrence following CRS plus HIPEC (n=838). The studies report recurrence rates are 26%-44% after first CRS/HIPEC and analyse the effectiveness of repeated CRS plus HIPEC intervention.

In Verwaal et al., 2004, 106 patients underwent cytoreduction and HIPEC. The progression-free interval, the location of the recurrence, and its treatment were recorded. Factors potentially related to survival after recurrences were studied.

Results

Sixty-nine patients had a recurrence within the study period (65%). For patients who had undergone a gross incomplete initial cytoreduction, the median duration of survival after recurrence was 3.7 months (standard error of the mean [SE], ± 0.3). If a complete cytoreduction had been accomplished initially, the median duration of survival after the recurrence was 11.1 months (SE,± 0.9). A shorter interval between HIPEC and recurrence was associated with shorter survival after treatment of recurrence (hazard ratio, 0.94; SE,± 0.02). After effective initial treatment, a second surgical debulking for recurrent disease resulted in a median survival duration of 10.3 months (SE, ± 1.9), and after treatment with chemotherapy it was 8.5 months (SE, 1.6). The survival was 11.2 months (SE, ± 0.5) for patients who received radiotherapy for recurrent disease. Patients who did not receive further treatment survived 1.9 months (SE, ± 0.3).
Authors’ conclusion

Treatment of recurrence after cytoreduction and HIPEC is often feasible and seems worthwhile in selected patients. Selection should be based mainly on the completeness of initial cytoreduction and the interval between HIPEC and recurrence.

WHSSC commentary

The study is limited by it’s retrospective, non-comparative and observational design. A clear relationship between completeness of cytoreduction and outcome is clearly shown.

In Sardi et al., 2013, a retrospective study of a prospective database of 294 patients with peritoneal carcinomatosis (PC) was conducted, of these 162 had PC of appendiceal origin. Twenty-six of these patients underwent 56 CRS/HIPEC. Survival and outcomes was analysed.

Results

The percentage of patients with pre-surgical PCI scores ≥ 20 for the first, second, and third CRS/HIPEC was 65, 65, and 25%, respectively. Complete cytoreduction (CC 0-1) at first, second, and, third surgeries was 96, 65 and 75%, respectively. The mean operating time was 10.1 h. There was no 30-day peri-operative mortality. Following the first, second, and third CRS/HIPEC 27, 42, and 50% experienced grade III complications, respectively. Mean follow up was 51, 28, and 16 months from the first, second, and third CRS/HIPEC, respectively. Overall survival rate for the first CRS/HIPEC was 100, 83, 54, and 46% at years 1, 3, 5 and 10, respectively; from the second CRS/HIPEC 91, 53, and 34% at 1, 3, and 5 years, respectively; and from the third CRS/HIPEC was 75% at one year.

Authors’ conclusion

Repeat CRS/HIPEC can lead to meaningful long term survival rates in patients with appendiceal peritoneal carcinomatosis with morbidity and mortality similar to those of the initial CRS/HIPEC.

WHSSC commentary

The study is limited by it’s retrospective, non-comparative and observational design.
Section criteria

The literature search identified 3 studies reviewing patient selection criteria for CRS plus HIPEC (de Silva and Sugarbaker., 2006; Iversen et al., 2013; Elias et al, 2014: n=365).

In de Silva and Sugarbaker, 2006, from a database of 156 patients with carcinomatosis from colorectal cancer, a retrospective analysis of data prospectively recorded in 70 patients with complete cytoreduction was performed. Eleven clinical and treatment factors were studied in univariate and multivariable analyses using survival as an end point.

Results

By univariate analysis, patients with peritoneal cancer index (PCI) of<20 had a median survival of 41 months compared with 16 months for patients with PCI>20 (p=0.004). The difference in negative versus positive lymph nodes was also significant; differences in survival that were improved but not significant were present for age greater than 30 years, mucinous histology, location within the colon versus rectum, and absence of an adverse factor such as cancer perforation or obstruction present at the time of primary cancer resection. Only PCI<20 versus PCI>20 and lymph node status were significant in the multivariable analysis.

Authors’ conclusion

Favourable longterm results of complete cytoreduction in patients treated for carcinomatosis are associated with a limited volume of carcinomatosis observed at the time of cytoreduction and in patients with negative lymph nodes at the time of primary operation.

WHSSC commentary

In Iversen et al., 2013, patients with peritoneal carcinomatosis from colorectal cancer or appendiceal cancer, pseudomyxoma peritonei or peritoneal mesothelioma referred to a single, national HIPEC centre were included prospectively between June 2006 and January 2012. From September 2010, preoperative evaluation also included a laparoscopy in patients deemed amenable to cytoreductive surgery and HIPEC after radiological evaluation, apart from those with pseudomyxoma peritonei with massive amounts of mucin.
Results

In the period before laparoscopic evaluation, 70 patients underwent laparotomy of whom 39 (56 per cent) completed cytoreductive surgery and HIPEC. After the introduction of laparoscopic assessment, diagnostic laparoscopy was planned in 45 patients and successful in 43. The laparoscopic evaluation excluded 18 patients from surgery because of extensive disease, among other reasons. Laparoscopy was uneventful and associated with no deaths. Twenty-seven patients were considered amenable to cytoreductive surgery and HIPEC based on laparoscopic findings, of whom 17 completed this treatment; the disease was unresectable in the remaining ten patients. Of 13 patients who were not eligible for laparoscopic evaluation and were subjected to cytoreductive surgery plus HIPEC, 11 completed the procedure. The overall completion rate of cytoreductive surgery and HIPEC increased to 70 per cent (28 of 40) after the introduction of laparoscopic evaluation.

Authors’ conclusion

Diagnostic laparoscopy was valuable in preoperative evaluation of the extent of peritoneal carcinomatosis, and improved patient selection for cytoreductive surgery and HIPEC.

WHSSC commentary

In Elias et al., 2014, Patients (n = 139) treated with CCRS plus HIPEC were prospectively verified and retrospectively analyzed. One hundred presented with SB involvement of different extents and at different locations.

Results

All the patients with a PCI ≥15 exhibited SB involvement. Five-year overall survival was 48% when the PCI was <15 vs 12% when it was ≥15 (p < 0.0001. The multivariate analysis retained two prognostic factors: PCI ≥15 (p = 0.02, HR = 1.8), and the involvement of area 12 (lower ileum) (p = 0.001, HR = 3.1). When area 12 was invaded, it significantly worsened the prognosis: 5-year overall survival of patients with a PCI <15 and area 12 involved was 15%, close to that of patients with a PCI ≥15 (12%) and far lower than that of patients with a PCI <15 and no area 12 involvement (70%).

Authors’ conclusion

A PCI greater than 15 appears to be a relative contraindication for treatment of colorectal PM with CRS + HIPEC. Involvement of the lower ileum is also a negative prognostic factor to be taken into consideration.
WHSSC commentary

The is a useful study describing the relationship between PCI index involvement of the lower ileum and outcome. The study is limited by it’s observational nature.

Quality of Life

The search strategy identified 8 studies that assessed quality of life (QOL) following CRS plus HIPEC in PM (Table x; n= 472; McQuellon et al., 2001; McQuellon et al., 2003; McQuellon et al., 2007; Schmidt et al., 2005; Duckworth et al., 2012; Tan et al., 2013; Chia et al., 2014).

The data of QOL is separated into two distinct QOL assessment based on the timing of the QOL assessment:

- Studies which assessed QOL pre-CRS plus HIPEC then post intervention (McQuellon et al., 2001; McQuellon et al., 2003; McQuellon et al., 2009; Schmidt et al., 2005);
- Studies which assess QOL 10 month – 3 years post CRS plus HIPEC (survivors), with or without a control group (McQuellon et al., 2003; Duckworth et al., 2012; Tan et al., 2013; Chia et al., 2014).

Table 18 summaries this data on QOL. Overall the studies generalise data for quality of life for a heterogeneous group of tumours subtypes with a number of well validated QOL instruments. There are concerns about generalising across tumour subtypes as clearly the natural progression of the respective disease subtypes if different and it is implausible that these differences would not have an impact on patient reported QOL.
Table 18 Summary of the QOL Studies for CRS Plus HIPEC

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of assessment</th>
<th>Tumour subtypes</th>
<th>QOL Instrument</th>
<th>Sample size</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-, peri-operative and post CRS plus HIPEC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McQuellon et al., 2001</td>
<td>2 weeks post surgery; 3-, 6- and 12 months</td>
<td>Appendiceal, colorectal, gastric</td>
<td>FACT-C</td>
<td>64</td>
<td>No</td>
</tr>
<tr>
<td>Schmidt et al., 2005</td>
<td>Baseline prior to surgery and 3, 6 and 12 months</td>
<td>Appendiceal, colorectal</td>
<td>EORTC QLQ-C30</td>
<td>67</td>
<td>No</td>
</tr>
<tr>
<td>Tuttle et al., 2006</td>
<td>Baseline, 4, 8 and 12 months</td>
<td>Appendiceal, colorectal, mesothelioma, gastric</td>
<td>FACT-C</td>
<td>35</td>
<td>No</td>
</tr>
<tr>
<td>McQuellon et al., 2007</td>
<td>Baseline prior to surgery and 3, 6 and 12 months</td>
<td>Appendiceal, colorectal, ovarian, mesothelium, gastric</td>
<td>FACT-C SF-36 CES-D ECOG BPI-SF</td>
<td>96</td>
<td>No</td>
</tr>
<tr>
<td><strong>Post CRC plus HIPEC: Survivorship QOL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McQuellon et al., 2003</td>
<td>&gt;3 years post-treatment</td>
<td>Appendiceal, ovarian, colorectal, peritoneal</td>
<td>FACT-C MOSQ CES-D LAS PSQ</td>
<td>17</td>
<td>No</td>
</tr>
<tr>
<td>Duckworth et al., 2012</td>
<td>12 months plus post-treatment</td>
<td>Ovarian, appendiceal, colorectal, mesothelioma</td>
<td>SF-36 FACT-C PSQI</td>
<td>102</td>
<td>No</td>
</tr>
<tr>
<td>Tan et al., 2013</td>
<td>6-18 months post-treatment</td>
<td>Ovarian, appendiceal, colorectal</td>
<td>EORTC QLQ-C30</td>
<td>27</td>
<td>Yes</td>
</tr>
<tr>
<td>Chia et al., 2014</td>
<td>16 months</td>
<td>Ovarian, appendiceal, colorectal</td>
<td>EORTC QLQ-C30</td>
<td>63</td>
<td>No</td>
</tr>
</tbody>
</table>

BPI-SF Brief Pain Inventory-Short Form; CES-D Centre for Epidemiologic Studies-Depression scale; EORTC QLQ-C30 FACT-C Functional Assessment of Cancer Therapy-Colon; LAS Life Appreciation scale; PSQ Psychosocial Concerns Questionnaire; SF-36 Short Form 36;

**Pre and post CRS plus HIPEC QOL**

McQuellon et al., 2001; Schmidt et al., 2005; McQuellon et al., 2009

In McQuellon et al., 2001, 64 patients with confirmed or suspected diagnosis of gastro-intestinal cancer including stomach, pancreas, hepatobiliary and colorectal cancer with peritoneal implants were enrolled in the study. Sixty-four patients completed the Functional Assessment of Cancer Therapy-Colon (FACT-C) scale and several other instruments at baseline. Forty-eight, 40, 39 and 31 patients were assessed at approximately 2 weeks post-surgery, and 3, 6 and 12 months respectively.
Results
There was a significant overall effect on the physical (P=0.0025), emotional (P<0.0001) and functional well-being (P=0.0044) subscales and the FACT-C (P=0.0076). Physical and functional well-being scores decreased at post-surgery follow-up and increased relative to baseline at 3, 6 and 12 months. Nineteen per cent, 46%, 59% and 74% of patients resumed greater than 50% of their normal activities post-operatively at 3, 6 and 12 months respectively. A percentage of patients reported depressive symptoms: baseline (28%), post-operatively (33%), 3 months (23%), 6 months (21%) and 12 months (29%).

Authors’ conclusion
CRC followed by IPHC was well tolerated. Most patients returned to baseline or better levels of functioning within 3 months post-treatment.

WHSSC commentary
The instruments used in the study were well validated although the heterogenous populations the instruments were applied in and the small size of the sub-group populations makes the results difficult to interpret.

In Schmidt et al., 2005, 67 patients with PC were operated with the aim of complete macroscopical cytoreduction followed by HIPEC (using cisplatin, mitomycin or mitoxantrone). Quality of life was assessed with the EORTC QLQ-C30 questionnaire.

Results
The patients had a variety of primary tumours, including appendix carcinomas (22/67). Mean operating time was 7 hours and complete cytoreduction was achieved in 58% of the patients. Overall morbidity was 34%. Post-operative mortality was 4.5%. The mean score for global health status of long-term survivors (20 questionnaires/25 patients) was 62.6 (73.3 for the control population, p=0.07). Functional status, particularly the role (56.4) and the social functioning (53.9) were impaired.

Authors’ conclusion
CRS plus HIPEC is associated with an increased morbidity and mortality. Complications are predominantly related to major surgery. Following this aggressive treatment, survivors may achieve a satisfactory quality of life.
WHSSC commentary

The instruments used in the study were well validated although the heterogeneous populations the instruments were applied in and the small size of the sub-group populations makes the results difficult to interpret.

In McQuellon et al., 2009, patients completed a questionnaire before and after surgery at 3, 6 and 12 months. The questionnaire consisted of basic demographic items as well as the Functional Assessment of Cancer Therapy-Colon Scale (FACT-C), SF-36 Medical Outcomes Study Health Survey, Center for Epidemiologic Studies-Depression Scale (CES-D), Brief Pain Inventory-Short Form, and ECOG Performance Status Rating. Time trends were assessed with mixed models (SAS PROC MIXED) so as to use all data and to account for missing data.

Results

Ninety-six patients (49% females, 9% African Americans) of an average age of 52.9 (SD = 12.5) years were assessed before surgery. PC originated in primary lesions of the appendix (n = 36); colon/rectum (n = 24); mesothelium (n = 9); ovary (n = 5); stomach (n = 4); and miscellaneous (n = 18). Quality of life (QOL) and pain scores improved from baseline to 12 months. Physical functioning changed over the 12-month study period with improvement recorded at 6 months. The percentage of patients reporting significant depressive symptom at each time point was; baseline = 32%; 3 months = 19%; 6 & 12 months = 24%.

Authors’ conclusions

Acceptable QOL, return of functional status, and reduced pain can be attained between 3 and 6 months following treatment although some deficits in general health remain. Depressive symptoms are common and should be monitored.

WHSSC commentary

The instruments used in the study were well validated although the heterogeneous populations the instruments were applied in and the small size of the sub-group populations makes the results difficult to interpret.

Post CRC plus HIPEC: Survivorship QOL

McQuellon et al., 2003; Duckworth et al., 2012, Tan et al., 2013 and Chia et al., 2014 assessed QOL of patients using the SF-36, FACT-C, PSQI and the EORTC QLQ-C30 between 10 months and 1.3 years post CRS plus HIPEC (n=192). In Tan et al., 2013, these results were matched against a cohort of disease-free cancer patients (n=393) not on active therapy but with good baseline performance status (ECOG 0 or 1). In McQuellon et al., 2003; Duckworth et al., 2012 and Chia et al., 2014, no attempt to match a control group was made.
In McQuellon et al. 2003 patients were interviewed by telephone with the following tools: (1) the Functional Assessment of Cancer Therapy-Colon (FACT-C), (2) the Short Form of the Medical Outcomes Study Questionnaire, (3) the Center for Epidemiologic Studies-Depression scale, (4) the Life Appreciation scale, (5) the Psychosocial Concerns Questionnaire, and (6) performance status rating.

Results
Seventeen (10 appendix, 5 large intestine, 1 ovarian, and 1 peritoneum) of 109 patients were interviewed from 3.1 to 8.0 years after treatment. Ten patients (62.5%) described their health as excellent or very good. No limitations on moderate activity were reported in 94% of cases. Paired t-tests were used to compare 10 patients who had baseline QOL data. FACT mean difference scores and P values (positive difference scores indicate improved QOL) were functional well-being: 4.9, P =0.01; physical well-being: 3.3, P =0.05; and FACT total: 14.3, P =0.02.

Authors’ conclusion

Long-term survival with good QOL is possible for selected patients with peritoneal carcinomatosis after cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy.

WHSSC commentary

The instruments used in the study were well validated although the heterogenous populations the instruments were applied in and the small size of the sub-group populations makes the results difficult to interpret.

In Duckworth et al. 2012, 102 patients living 12 plus months post-treatment completed a survey including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), Functional Assessment of Cancer Therapy-Colon (FACT-C), and Pittsburgh Sleep Quality Index.

Results

SF-36 Physical Component scores were significantly lower than general population norms (46.7, z= -2.943, P=0.003), while Mental Component scores were significantly higher (53.6, z=4.208, P ≤ 0.001). FACT scores were higher than general FACT normative scores. The majority (56%) of these survivors reported significant sleep quality impairment.
Authors’ conclusion
Although most HRQOL scores were comparable to or higher than those of the general population, long-term physical and functional deficits remain. These deficits, along with the poor sleep quality of recipients, may be improved by survivorship programs or targeted psychosocial interventions.

WHSSC commentary
This study highlights that residual deficits remain in survivors following CRS plus HIPEC. The instruments used to assess QOL are well validated. No comparative data was available from the study.

In Tan et al., 2013, patients who completed CRS + HIPEC 6-18 months previous to the study (27 patients) were enrolled. QOL was measured via the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaires. The scores were compared with a group of 393 disease-free cancer patients, not on active treatment, who had ECOG scores of either 0 or 1. The 1-sample t test was used to compare differences in QOL scores between the 2 groups.

Results
A total of 27 patients were analysed, of which 22 (81 %) were females. Median age was 51 years (15-59 years). CRS + HIPEC were performed for ovarian cancer in 15 patients (55 %), appendiceal carcinoma in 5 patients (19 %), and colorectal carcinoma in 4 patients (15 %). The median intraoperative peritoneal carcinomatosis index (PCI) score was 15 (2-31) while the completeness of CC score was 0 and 1 in 25 and 2 patients, respectively. The median duration after CRS + HIPEC was 10 months (6-16 months). Global health status and functional and symptom scores were largely similar between patients after CRS + HIPEC and the control group. Cognitive functioning scores and fatigue scores were significantly better in the group after CRS + HIPEC (p = 0.014 and 0.04).

Authors’ conclusion
QOL after CRS and HIPEC can be equivalent to that of well-functioning, disease-free cancer patients.

WHSSC commentary
QOL was assessed in a heterogenous population in a small sample size. The QOL instruments used were well validated. Comparative data was available although it is unclear how well matched the cohorts were.
In Chia et al., 2014, 63 patients who had CRS and HIPEC from 2001 to 2012 and who were still alive and on follow up were included. The EORTC-QLQ-C30 was administered to the patients.

Results
Median age was 53 years (14-71). 44% had ovarian primaries, 21% had appendiceal primaries and 19% had colorectal primaries. Median follow-up was 1.08 years (0.06-9.8). The median time from surgery to the questionnaire was 1.3 years (0.24-10.18). There was no statistical difference in scores when comparing by age, gender, recurrence, gender, PCI score, presence of a complication and type of primary cancer. Scores were highest less than 6 months after surgery, dropped subsequently but rose again after 2 years. Our patients had better scores compared to a control group of outpatient cancer patients at our institution as well as the reference EORTC group.

Authors’ conclusion
In keeping with previous quality of life studies done for CRS and HIPEC patients, we have shown that our patients can achieve a good quality of life after CRS and HIPEC even with recurrent disease.

WHSSC commentary
The instruments used in the study were well validated although the heterogenous populations the instruments were applied in and the small size of the sub-group populations makes the results difficult to interpret.
Cost Effectiveness

The literature search only identified one study assessing the cost-effectiveness of CRS plus HIPEC based on consecutive patients who underwent 159 CRS plus HIPEC procedures (Chua et al., 2010).

Patient Selection

From June 2002 to June 2008, consisting of 6 financial years, a total of 159 procedures of CRS and HIPEC were performed in 136 consecutive patients with peritoneal surface malignancy at the St George Hospital, Sydney, Australia. Evaluation for suitability to undergo CRS and HIPEC was made during a twice weekly meetings where patients were presented for discussion and imaging results (computed tomography [CT] scans, CT-angiogram of the liver and positron emission tomography scans) were studied. These meetings are attended by a multidisciplinary team comprising of a surgical oncologist, medical oncologist, radiologist, intensivist, team nurse, administration, and research staff.

Inclusion criteria include being >18 and ≤80 years old, good performance status (World Health Organization Performance Status ≤2), a histologic diagnosis of a peritoneal surface malignancy. Patients with extra-abdominal metastasis were excluded. Management was by a standardized treatment protocol, which includes CRS and HIPEC and in some cases, additional early postoperative intraperitoneal chemotherapy (EPIC) was administered depending on disease type. A signed informed consent was obtained from every patient.

Cytoreductive Surgery

All procedures were performed by the same surgical team, led by a single surgeon, using Sugarbaker peritonectomy procedures. Briefly, a midline laparotomy incision was performed, the volume and extent of disease were recorded using the Peritoneal Cancer Index (PCI). The aim in all patients was to remove all visible intraperitoneal and visceral tumor deposits. Peritonectomy procedures include total anterior parietal peritonectomy, greater omentectomy with or without splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, and lesser omentectomy with or without cholecystectomy. Visceral resections included rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy, and small bowel resection. These were performed on sites where there was visible evidence of disease. CRS was performed by using a ball-tip electrocautery device using maximum electrical power to achieve complete cytoreduction. All sites and volumes of residual disease following CRS were recorded prospectively using the Completeness of Cytoreduction (CC) score. CC0 indicates that no macroscopic residual cancer remained; CC1, that no nodule 2.5 mm in diameter remained; CC2, that nodules between 2.5 mm and 2.5 cm in diameter remained;
and CC3, that nodules _2.5 cm in diameter remained.

**Perioperative Intraperitoneal Chemotherapy (PIC)**

After cytoreduction, HIPEC was performed by instillation of a heated chemoperfusate into the abdomen using the coliseum technique at approximately 42°C for 90 minutes. For gastrointestinal malignancies, mitomycin C (10 –12.5 mg/m2) was used. For peritoneal mesothelioma and ovarian malignancies, cisplatin (50 mg/m2), and doxorubicin (12 mg/m2) were used. Patients with pseudomyxoma peritonei and colorectal peritoneal carcinomatosis were scheduled to receive EPIC, 5-fluorouracil (650–800 mg/m2 per day), on postoperative day 1 to 5 unless there were clinical contraindication.

**Prospective Database**

The prospective database was designed specifically to record and evaluate the perioperative outcomes of patients with peritoneal surface malignancy. For each patient, a postoperative complication from Grade I to IV with increasing severity was assigned based on the National Cancer Institute’s Common Toxicity Criteria. Treatment-related mortality was defined as death within 30-days following treatment. All patients were followed prospectively at monthly intervals for the first 3 months and at 6 monthly intervals thereafter until death.

**Cost Analysis of CRS and HIPEC**

The cost of CRS and HIPEC per patient was evaluated by the hospital’s Network Manager Performance Unit that is responsible for providing activity performance and costing information and analysis to support performance management of health service. Direct cost of treatment is defined as the cost related to the service at the point of service delivery. The total direct cost per patient include clinical cost, which are medical costs associated with the patient, operating theatre costs, procedure room costs, pathology costs, imaging costs, cost of ward care, cost of allied healthcare, pharmaceutical costs, and ICU costs. The total cost per patient include other cost related to the authority of the New South Wales Health System, for example prosthesis, which are allocated using a disease-related group weighted based average, depreciation costs for hospital assets, and overhead costs that are indirectly related to patient care such as linen service, food catering, human resources, etc. The total cost per patient therefore has both direct and indirect components related to the patient’s care. The total cost also includes cost of managing complications and treatment failures.

**Cost Analysis and Outcomes From Standard Treatment**

Estimates of the cost of treatment for each peritoneal surface malignancy disease types were obtained from a publication from the Australian Institute of Health and Welfare (AIHW), the designated national health and welfare statistics and information agency in Australia. From this document, the estimated average lifetime
treatment cost, which is the treatment costs for the year 2000 to 2001 divided by the number of new cases in 2001 to derive an estimate of lifetime treatment cost per incident cases as an approximate based on the assumptions that incidence and mortality rates are steady over time showed that for colorectal cancer, the total lifetime cost of treatment was AUD $18,246.18 Cost estimates for other types of cancer were not available. Estimated survival time with standard treatment for this cancer type as reported in the literature is about 6 months.

**Statistical Analysis**

Descriptive statistics were generated for all measures, including means, ranges, and standard deviations for continuous variables and frequencies and proportions for categorical data. Continuous variables were compared using the student t test and categorical variables were compared using the Chi² analysis or Fisher exact test where appropriate. Survival was calculated from the date of operation to last known date of follow-up or date of death using the Kaplan-Meier method. Effectiveness was defined as months of overall survival after treatment. Costs were calculated as total costs per strategy. Cost-effectiveness was defined as cost per month of survival and reported as the costs per life year (LY) with the survival being the time from operation till death. A comparison of the incremental costs, incremental survival, and ICER between CRS and HIPEC and standard treatment was performed and reported in cost per life year saved (LYS). The cost is reported in AUD $ and are also reported in USD $ applying a financial exchange rate of USD $1 = AUD $1.30 in the tables. All statistical analyses were performed using the SPSS for Windows version 15.0 (SPSS, Munich, Germany). P ≤ 0.05 was considered significant.

**Results**

**Patient Demographics**

There were 159 procedures of CRS and HIPEC performed on 136 patients with peritoneal surface malignancy. Of total, 59 (43%) were men and 77 (57%) were women. The mean age was 52 (s.d. = 12) years. About 59 (43%) patients had pseudomyxoma peritonei, 17 (13%) patients had appendix adenocarcinoma, 34 (25%) patients had colorectal adenocarcinoma, 15 (11%) patients had peritoneal mesothelioma, and 11 (8%) patients had other peritoneal surface malignancies, such as small bowel adenocarcinoma and ovarian cancer.

**Clinical Characteristics**

Of the 159 procedures, 23 (14%) were repeat CRS and HIPEC treatments performed in 19 patients for recurrent or persistent disease. About 16 patients underwent 2 repeat CRS, 2 patients underwent 3 repeat CRS, and 1 patient underwent 4 repeat CRS. The median PCI was 16, with a mean of 17 (9). Of total, 128 (81%) procedures performed were CC0 cytoreduction, 26 (16%) procedures performed were CC1 cytoreduction, and 5 (3%) procedures performed were CC2 cytoreduction. All 159 (100%) cytoreductive surgical procedures were combined with
intraoperative HIPEC. In addition, 110 (69%) CRS and HIPEC procedures were further combined EPIC.

**Morbidity and Mortality**

The median duration of the procedure was 9 hours, with a mean of 10 (4) hours. The median length of ICU admission post-procedure was 2 days, with a mean of 5 (9) days. The median total length of hospital stay was 23 days, with a mean of 33 (31) days. The median amount of blood transfused was 4 units, with a mean of 6 (7) units. About 83 (52%) procedures were completed without or only had minor (Grade I/II) postoperative complications. About 76 (48%) procedures resulted in major (Grade III/IV) postoperative complications. There was one death within 30-days following treatment resulting in a treatment-related mortality (Grade V) rate of 0.06%.

**Survival Outcomes**

For the cohort of 136 patients, the median follow-up period was 30 (range, 0–86) months, the overall median survival was 65 months, with a 1-, 3-, and 5-year survival rate of 92%, 68%, and 52%, respectively (Figure 23).

**Figure 23.** Overall survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancy (n= 136).
The survival analysis included patients who were classified as postoperative mortality. After CRS and HIPEC, the median survival of patients with peritoneal surface malignancy from appendix cancer (n = 17) was 48 months, colorectal cancer (n = 34) was 33 months, pseudomyxoma peritonei (n = 59) was not reached, peritoneal mesothelioma (n = 15) was 49 months, and other peritoneal surface malignancies (n = 11) was 35 months (Figure 24).

Cost of CRS and HIPEC for Peritoneal Surface Malignancy

Of 159 procedures, the financial years for which the procedures were performed were 10 (6%) in year 02/03, 18 (11%) in year 03/04, 26 (16%) in year 04/05, 33 (21%) in year 05/06, 39 (25%) in year 06/07, and 33 (21%) in year 07/08. The total cost was AUD $10,556,463 with AUD $663,275 (6%) comprising of clinical costs, AUD $2,275,881 (22%) comprising of operating theater cost, AUD $269,297 (3%) comprising of pathology costs, AUD $211,664 (2%) comprising of imaging cost, AUD $2,396,600 (23%) comprising of cost of ward care, AUD $155,955 (2%) comprising of allied healthcare cost, AUD $703,081 (7%) comprising of pharmaceutical cost,
AUD $272,238 (3%) comprising of prosthesis cost, AUD $264,495 (3%) comprising of depreciation cost, AUD $646,137 (6%) comprising of ongoing costs, and AUD $2,699,047 (26%) comprising of ICU cost (Figure 25). The average cost per procedure over the 6 financial years was AUD $66,456.

Figure 25. Component costs as a percentage of total expenditure for 159 procedures of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Cost Benefit Analysis of CRS and HIPEC for Peritoneal Surface Malignancies

The average cost of CRS and HIPEC per patient for appendix cancer is AUD $88,423 (range, AUD $23,933–AUD $299,145), for colorectal cancer is AUD $66,148 (range, AUD $26,079–AUD $409,666), for pseudomyxoma peritonei is AUD $92,308 (range, AUD $11,562–AUD $501,144), for peritoneal mesothelioma is AUD $55,062 (range, AUD $23,261–AUD $94,104), and for other peritoneal surface malignancies is AUD $44,668 (range, AUD $31,592–AUD $70,026).

From the AIHW data, given that the cost of standard treatment for colorectal cancer is AUD $18,246 for an estimated survival time of 6 months. The incremental cost when comparing standard treatment to that for colorectal cancer is (AUD $66,148 - $18,246 - $47,902) with a survival gained of (33 - 6 - 27 months). Hence, the cost per life year saved from standard treatment would be estimated to range from AUD $21,290/LYS.

Based on the survival results from CRS and HIPEC together with the total cost of treatment, calculated by dividing the total cost and the survival time, the analyzed
cost per life year was AUD $37,737/LY for appendix cancer, AUD $29,757/LY for colorectal cancer, AUD $29,559/LY for pseudomyxoma peritonei, AUD $20,521/LY for peritoneal mesothelioma, and AUD $22,091/LY for other peritoneal surface malignancies. Table 20 for conversion in UK £.

Table 20. Conversion of results from AUS $ to UK £ (historical conversion rate 0.393027)

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>AUS $/ Life year</th>
<th>UK£/Life year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendiceal</td>
<td>37,737</td>
<td>14,831</td>
</tr>
<tr>
<td>Colorectal</td>
<td>29,757</td>
<td>11,633</td>
</tr>
<tr>
<td>PMP</td>
<td>29,599</td>
<td>11,633</td>
</tr>
<tr>
<td>Peritoneal surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malignancies</td>
<td>20,521</td>
<td>8,009</td>
</tr>
</tbody>
</table>

Authors’ conclusion
This complex surgical treatment results in significant increases in medical costs with a parallel increase in survival for a disease that has been poorly treated, and hence may be considered as cost-effective given the observed life years gained.

WHSSC Commentary
This was the only study identified that assessed the cost-effectiveness of CRC plus HIPEC in PM. The data on clinical effectiveness used to calculate cost benefit was based on non comparative data of the effectiveness of CRS plus HIPEC (with small samples in each tumour sub-type) that could be a source of bias in the analysis. The study consistently underestimated the clinical effectiveness of standard care and potentially overestimated CRS plus HIPEC as a significant proportion of the CRS plus HIPEC group also had additional EPIC. There was no evidence that the study took into consideration the high recurrence rates associated with CRS plus HIPEC in their modelling.

There was an acceptable approach to the collection of data on costs and the calculation of costs. There is no evidence that either cost or benefits were discounted over time and limited evidence of modelling over an acceptable time horizon. The approach used was deterministic rather than probabilistic. The cost benefit analysis was based on a calculated cost per life year approach which excluded known data on QOL post CRS plus HIPEC.
Acknowledgements

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References to studies

**Baram HJ 2014**

**Baratti D 2014**

**Bijelic L 2007**

**Bloemendaal AL 2005**

**Brücher BL 2012**
Canda AE 2013

Cao C 2009

Cashin PH 2014

Chia CS 2014

Chua TC 2010

Cunningham D 2010
**de Cuba EM 2014**

**de Silva RG 2006**

**Duckworth KE 2012**

**Elias D 2009**

**Elias D 2014**

**Franko J 2010**
Glehen O 2004

Glehen O 2004b

Glockzin G 2009

Hansson J 2009

Hompes D 2012

Huang CQ 2013
**Iversen LH 2013**


**Jimenez W 2014**


**Kuijpers AM 2013**


**Mahteme H 2004**


**McQuellon RP 2001**

McQuellon RP 2003


McQuellon RP 2007


Mirnezami R 2014


Nikolic S 2014


Omohwo C 2009


Passot G 2013

**Piso P 2009**


**Prada-Villaverde A 2014**


**Ripley RT 2010**


**Rivard JD 2014**


**Sadeghi B 2000**

Sardi A 2013

Schmidt U 2005

Sugarbaker PH 1999

Tan WJ 2014

Tuttle TM 2006

Verwaal VJ 2003

Verwaal VJ 2004a
Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H and Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with

**Verwaal VJ 2004b**


**Verwaal VJ 2005**


**Verwaal VJ 2008**


**Yan TD 2006**


**Witkamp AJ 2001**


**Appendix 1 (See Spreadsheet)**