

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedure overview of cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Peritoneal carcinomatosis is an advanced form of cancer found in the peritoneal cavity (the space between the two membranes that separate the organs in the abdomen from the abdominal wall). This type of cancer happens when cancers from the appendix, bowel, rectum or ovaries spread. It is associated with short survival and poor quality of life, and may lead to bowel obstruction, accumulation of fluid in the peritoneal cavity and pain.

Cytoreduction surgery involves removing all of the visible (macroscopic) tumour. During the same operation, the peritoneal cavity is flushed with heated chemotherapy fluid with the aim of eliminating any microscopic traces of disease left behind.

## Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

## Date prepared

This overview was prepared in May 2009.

## Procedure name

- Cytoreduction surgery (CRS) followed by hyperthermic intraoperative peritoneal chemotherapy (HIPEC) for peritoneal carcinomatosis

## Specialty societies

- Association of Cancer Surgeons
- British Society of Gastroenterology
- Association of Coloproctology of Great Britain and Ireland

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- British Association of Surgical Oncology (BASO)
- British Gynaecological Cancer Society

## Description

### ***Indications and current treatment***

Peritoneal metastases commonly result from the regional spread of gastrointestinal, gynaecological and other malignancies. Peritoneal carcinomatosis is an advanced form of cancer associated with short survival and poor quality of life, which may lead to bowel obstruction, ascites (fluid in the peritoneal cavity) and pain.

There is no curative treatment. Current standard treatment uses systemic chemotherapy and/or surgery for short-term palliation of complications such as bowel obstruction.

### ***What the procedure involves***

This procedure was developed by Paul Sugarbaker at the Washington Cancer Institute (Washington, DC, USA). The aim of cytoreduction surgery (CRS) is to remove all macroscopic tumour using a laparotomy approach performed under general anaesthesia. Non-essential involved organs and peritoneum may also be removed. The surgery may include:

- removal of the right hemicolon, spleen, gall bladder, greater and lesser omentum, and parts of the stomach
- stripping of the peritoneum from the pelvis and diaphragm
- stripping of tumour from the surface of the liver
- removal of the uterus and ovaries in women
- removal of the rectum in some cases.

Although the aim of CRS is to remove all macroscopic tumour, microscopic, and often residual macroscopic tumour may be left behind.

After the CRS is completed, the abdomen is perfused with chemotherapy solution heated to between 40 and 43°C (above 46°C is lethal). The fluid is perfused within the abdomen for 60–120 minutes and then drained from the abdomen prior to closure. A further course of systemic or intraperitoneal chemotherapy may be administered after the surgery.

Intraoperative intraperitoneal administration of chemotherapy allows the drug to be distributed uniformly to all surfaces of the abdomen and pelvis. Potential advantages of heating the perfusion fluid are that it increases drug penetration and the cytotoxic effect of drugs such as mitomycin C and cisplatin. This part of the procedure is generally called HIPEC (hyperthermic intraperitoneal chemotherapy), but in the past has been known as HIIC (heated

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intraoperative intraperitoneal chemotherapy), IPCH (intraperitoneal chemotherapy) and IPHC (intraperitoneal hyperthermic chemotherapy).

Early postoperative intraperitoneal chemotherapy (EPIC) is often used after CRS, including after HIPEC. The chemotherapy agent is administered intraperitoneally, generally for 4–5 days following surgery and at normal temperature.

### ***List of studies included in the overview***

This overview is based on 1,717 patients from one systematic review<sup>1</sup> (containing 1 non-randomised comparative study and 13 case series), 1 randomised controlled trial (RCT)<sup>2</sup>, 4 non-randomised comparative studies<sup>3,4,5,6</sup> and one case series<sup>7,8</sup>. An additional 12 case series<sup>9,10,11,12,13,14,15,16,17,18,19,20</sup> of 1,569 patients provided detail on other rare but serious adverse events.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A. Studies with a sample size of less than 50 have been excluded from appendix A.

### ***Efficacy***

#### **Survival**

A systematic review of 291 patients (ovarian cancer) reported an overall median survival of 21.9–54 months (5 studies) and a mean survival of 31.5–48 months (3 studies)<sup>1</sup>.

An RCT (colorectal cancer) compared 54 patients who were treated with cytoreduction and HIPEC plus systemic chemotherapy with 51 patients treated with standard systemic chemotherapy. Patients in the HIPEC group had a significantly higher disease-specific survival of 22.2 months compared with 12.6 months in the standard treatment group ( $p = 0.028$ )<sup>2</sup>.

A non-randomised comparative study (colorectal cancer) compared 271 patients treated with cytoreduction and HIPEC with 123 patients treated with cytoreduction and EPIC and 112 patients with cytoreduction and HIPEC plus EPIC. This study reported no significant difference in median survival between groups (19.2 months, 19.2 months and 21.6 months respectively,  $p = 0.61$ )<sup>3</sup>.

A non-randomised comparative study compared 121 patients (colorectal cancer) treated with cytoreduction and HIPEC with 101 patients (hepatic metastases) treated with hepatic resection. Median survival was reported to be 16.5 months (95% confidence interval [CI] 14.7–20.8 months) in the HIPEC group compared with 40.1 months (95% CI 34–58.3 months) in the resection group<sup>4</sup> (significance level not stated).

A non-randomised comparative study (colorectal cancer) compared 48 patients treated with cytoreduction and HIPEC plus systemic chemotherapy  
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and 48 patients treated with palliative chemotherapy. A significantly higher median survival of 62.7 months was reported in the HIPEC group compared with 23.9 months in the palliative chemotherapy group ( $p < 0.05$ )<sup>6</sup>.

A case series of 460 patients with a mixture of different cancers treated with cytoreduction and HIPEC reported an overall median survival of 22.2 months<sup>7</sup>.

### 5 year survival

A systematic review of 291 patients (ovarian cancer) reported a 5-year survival rate of 12-63.4% (6 studies)<sup>1</sup>.

An RCT of 105 patients reported a 5-year survival rate of 45% in the HIPEC group for those who achieved complete cytoreduction<sup>2</sup>.

A non-randomised comparative study of 506 patients reported 5-year overall and disease-free survival rates of 19% and 10% respectively<sup>3</sup>.

A non-randomised comparative study of 222 patients reported a 5-year survival rate of 12.5% in the HIPEC group (colorectal cancer) compared with 33.9% in the resection-only group (hepatic metastases)<sup>4</sup>.

A non-randomised comparative study of 96 patients reported a significantly higher 5-year survival rate of 51% (95% CI 36–65%) in the HIPEC group compared with 13% (95% CI 6–26%) in the palliative chemotherapy group ( $p < 0.05$ )<sup>4</sup>.

A non-randomised comparative study of 37 patients with appendiceal cancer (patients received either HIPEC or EPIC or both following cytoreduction) reported an overall 5-year survival rate of 56% (95% CI 34–77%)<sup>5</sup>.

A case series of 460 patients who received CRS plus HIPEC reported a 5-year survival rate of 27.8%<sup>7</sup>.

### **Quality of life**

A case series of 96 patients with a mixture of different cancers and treated with cytoreduction and HIPEC reported a significant reduction in depression 1 year after surgery on the Centre for Epidemiologic Studies Depression Scale. Mean score of 13.8 prior to surgery dropped to 10.6 after 1 year ( $p=0.024$ )<sup>8</sup>. A reduction in the proportion of patients in severe pain (score 8–10 on the Brief Pain Inventory) from 17% (16/95) at baseline to 8% (3/37) at 3 months was also reported. The study highlighted a significant increase in overall quality of life measured by the Functional Assessment of Cancer Therapy–Colon scale with a mean score prior to surgery of 101 increasing to 111.1 after 1 year ( $p = 0.008$ ). In addition, the Short Form-36, a generic quality of life questionnaire, indicated that physical functioning (mean score increased from 69.5 to 80 at 6 months) problems with daily activities as a result of physical functioning (mean score increased from 36.3 to 53 at 1 year;  $p = 0.016$ ) and bodily pain (mean score increased from 64.8 to 81.5 at 1 year;  $p = 0.0007$ ) had significantly improved<sup>8</sup>.

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## **Safety**

### **Postoperative mortality**

An RCT of 105 patients reported a mortality rate of 7.4% (4/54) in the HIPEC group<sup>2</sup>.

A non-randomised comparative study of 506 patients reported a postoperative mortality rate of 4% (20/506)<sup>3</sup>. Digestive fistula was involved in 7 of the 20 deaths (35%).

A non-randomised comparative study of 222 patients reported no significant difference in postoperative mortality rate between the two groups: 5.5% (7/121) in the HIPEC group compared with 4.2% (4/101) in the resection group ( $p = 0.71$ )<sup>4</sup>.

A case series of 460 patients reported a 30-day mortality rate of 4.8% (22/460)<sup>7</sup>.

### **Postoperative morbidity**

A systematic review of 291 patients (ovarian cancer) reported significant morbidity requiring return to intensive care unit, an invasive procedure or return to the operating room in 5–36% of patients (8 studies)<sup>1</sup>.

#### Bowel perforation / leak

A systematic review of 291 patients (ovarian cancer) reported a bowel perforation / leak rate of 2.5-12% (7 studies)<sup>1</sup>.

#### Fistula

A systematic review of 291 patients (ovarian cancer) reported a fistula rate of 3.5–15% (3 studies)<sup>1</sup>. An RCT of 105 patients reported a gastrointestinal fistula rate of 14.6% (7/48) in the HIPEC group<sup>2</sup>. Two non-randomised comparative studies of 506 and 37 patients reported a digestive fistula rate of 8.3% (42/506)<sup>3</sup> and fistula (not otherwise described) 16% (6/37)<sup>5</sup> respectively.

#### Sepsis

A systematic review of 291 patients (ovarian cancer) reported a sepsis rate of 5–8% (3 studies)<sup>1</sup>. An RCT of 105 patients reported 3 deaths (2.9%) from abdominal sepsis; 2 within 40 days of surgery and 1 more than 3 months after surgery<sup>2</sup>. A non-randomised comparative study of 506 patients reported a systemic sepsis rate of 2% (10/506) and a line sepsis rate of 1% (5/506)<sup>3</sup>.

#### Pancreatitis

An RCT of 105 patients reported 1 patient with pancreatitis in the HIPEC group (2.1%)<sup>2</sup>. A case series of 241 patients reported 1 patient with pancreatitis after surgery<sup>9</sup>.

#### Acute renal failure

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A non-randomised comparative study of 506 patients reported 1 death due to acute renal failure<sup>3</sup>. A case series of 59 patients reported acute renal failure in 3.4% (2/59)<sup>20</sup>. A case series of 140 patients reported acute renal failure requiring dialysis in an intensive care unit in 0.7% (1/140)<sup>14</sup>.

#### Haematological toxicity

A systematic review of 291 patients (ovarian cancer) reported a hematological toxicity rate of 0–15% (6 studies)<sup>1</sup>. A non-randomised comparative study of 506 patients reported hematological toxicity in 2.4% (12/506)<sup>3</sup>. A case series of 96 patients reported grade 3 neutropenia in 3.1% (3/96)<sup>12</sup>. A case series of 140 patients reported chemotherapy related neutropenia in 4% (5/140)<sup>14</sup>. A case series of 122 patients reported 1 case of haemolytic–uraemic syndrome<sup>15</sup>. A case series of 106 patients reported grade 4 thrombocytopenia or neutropenia in 11% (12/106)<sup>16</sup>.

#### Cardiorespiratory

A non-randomised comparative study of 506 patients reported 5 deaths (1%) due to respiratory complications, and respiratory distress in a further 1.6% (8/506)<sup>3</sup>. A case series of 241 patients reported acute respiratory distress syndrome in 1 patient and arrhythmia in 2 patients after surgery<sup>9</sup>. A case series of 59 patients reported arrhythmias in 3.4% (2/59)<sup>20</sup>. A case series of 207 patients reported myocardial necrosis in 1 patient after surgery<sup>10</sup>. Case series of 200, 174, 140 and 64 patients reported pneumothorax in 2.5% (5/200)<sup>13</sup>, 2% (3/174)<sup>11</sup>, 7% (10/140)<sup>14</sup> and 2% (1/64)<sup>18</sup> respectively. A case series of 122 patients reported 1 case of myocardial infarction<sup>15</sup>.

#### Thromboembolic

An RCT of 105 patients reported 1 death (2.4%) in the HIPEC group from a massive lung embolus. A further 4.2% (2/48) of patients in the HIPEC group had a pulmonary embolism within 3 months of surgery<sup>2</sup>. A non-randomised comparative study of 506 patients reported pulmonary embolism in 0.4% (2/506)<sup>3</sup>. Case series of 207, 200, 174, 122, 100 and 64 patients reported pulmonary embolism in 1.3% (3/207)<sup>10</sup>, 0.5% (1/200)<sup>13</sup>, 5.8% (4/174)<sup>11</sup>, 2.5% (3/122)<sup>15</sup>, 4% (4/100)<sup>17</sup> and 1.6% (1/64)<sup>18</sup> respectively.

Case series of 207, 200, 100 and 64 patients reported deep vein thrombosis in 1.8% (4/207)<sup>10</sup>, 1% (2/200)<sup>13</sup>, 5% (5/100)<sup>11</sup> and 3% (2/64)<sup>18</sup> respectively. A case series of 60 patients reported venous thromboembolism in 10% (6/60)<sup>19</sup>.

#### Neurological

A case series of 241 patients reported prolonged paralysis in 1.2% (3/241)<sup>9</sup>.

### **Reoperation rate**

A systematic review of 291 patients (ovarian cancer) reported a reoperation rate of 0–16% (9 studies)<sup>1</sup>. A non-randomised comparative study of 506 patients reported a reoperation rate of 10.7% (54/506)<sup>3</sup>.

## Literature review

### *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to complete cytoreduction and heated intraoperative intraperitoneal chemotherapy (Sugarbaker technique) in patients with peritoneal carcinomatosis. Searches were conducted of the following databases, covering the period from their commencement to 13/05/2009: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution process that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

**Table 1 Inclusion criteria for identification of relevant studies**

Characteristic	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.
Patient	Patients with peritoneal carcinomatosis
Intervention/test	Complete cytoreduction and heated intraoperative intraperitoneal chemotherapy (Sugarbaker technique)
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

### ***Existing assessments of this procedure***

There were no published assessments from other organisations identified at the time of the literature search.

### ***Related NICE guidance***

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

#### **Interventional procedures**

- Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique). NICE interventional procedures guidance 56 (2004). Available from [www.nice.org.uk/IPG56](http://www.nice.org.uk/IPG56)

#### **Clinical guidelines**

- Guidance on cancer services: Improving outcomes in colorectal cancer (manual update). NICE clinical guideline CSGCC (2004). Available from [www.nice.org.uk/CSGCC](http://www.nice.org.uk/CSGCC)



**Table 2: Summary of key efficacy and safety findings on cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy (HIPEC) for peritoneal carcinomatosis**

Abbreviations used: CRS / CS= cytoreduction surgery; EPIC = early postoperative intraperitoneal chemotherapy; HIIC = heated intraoperative intraperitoneal chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; IPCH = intraperitoneal chemotherapy; IPHC = intraperitoneal hyperthermic chemotherapy			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Bijelic et al (2007)<sup>1</sup></p> <p>Study type: <b>Systematic review (including 1 non-randomised controlled study and 13 case series)</b></p> <p>Country: International</p> <p>Study period: 1996–2006</p> <p>Study population: patients with advanced primary (International Federation of Gynecology and Obstetrics stage III and IV), persistent or recurrent ovarian cancer.</p> <p>n = <b>291</b></p> <p>Age: NR</p> <p>Sex: all female</p> <p>Inclusion criteria: English-language studies</p> <p>Exclusion criteria: Studies restricted to pharmacological data. Reports on low-grade (borderline) tumors and appendiceal malignancies with ovarian spread,</p> <p>Technique: IPCH given intraoperatively and/or in the immediate postoperative period (1–5 days) following an attempt at maximal surgical cytoreduction. Seven (50%) studies used an open method to administer HIIC and 7 used a closed method. In 4 of the studies, EPIC was also administered to some or all patients. The chemotherapy agent used was heated to different temperatures (39–44 °C) and different chemotherapy drugs (e.g. paclitaxel, mitomycin C, cisplatin, doxorubicin and carboplatin) were used at different doses in the studies.</p> <p>Follow-up: up to 5 years (median: 13.7–30 months [9 studies])</p> <p>Conflict of interest: None</p> <p>Study supported by the Foundation for Applied Research in Gastrointestinal Oncology</p>	<p><b>Rate of complete cytoreduction</b></p> <p>According to Sugarbaker classification (tumour residuals &lt;2.5 mm ): - 57 to 100% (5 studies)</p> <p>&lt;2 mm: 9/19 (47%) (1 study)</p> <p>&lt;5 mm: 15/19 (79%); 5/5 (100%) (2 studies)</p> <p>&lt;1 cm: 48/57 (84%); 28/30 (93%) (2 studies)</p> <p>&lt;1.5 cm: 12/20 (60) (1 study)</p> <p>&lt;2 cm: 12/25 (48%)</p> <p>2 studies did not report the success of cytoreduction.</p> <p>Impact of CRS on survival: 7 studies reported a significant relationship between improved survival and complete cytoreduction.</p> <p><b>Survival</b></p> <p><u>Overall:</u></p> <p>Median: 21.9–54 months (5 studies); mean: 31.5–48 months (3 studies)</p> <p><u>For optimal cytoreduction only:</u></p> <p>Median: 29–55.9 months (3 studies)</p> <p>Mean: 66 months (1 study)</p> <p><u>Median disease/progression free survival:</u></p> <p>10.5–26 months (4 studies)</p> <p><u>2 year survival:</u></p> <p>60–71% (4 studies)</p> <p><u>3 year survival:</u></p> <p>20–63% (6 studies)</p> <p><u>5 year survival:</u></p> <p>12–63.4% (6 studies)</p> <p><b>Reoperation rate</b></p> <p>0–16% (9 studies)</p>	<p>Mortality (time period not defined): median 3%, range 0–10% (14 studies)</p> <p>Hematological toxicity: 0–15% (6 studies)</p> <p>Renal toxicity: 0–10% (7 studies)</p> <p>Bowel perforation / leak: 2.5–12% (7 studies)</p> <p>Fistula: 3.5–15% (3 studies)</p> <p>Sepsis: 5–8% ( 3 studies)</p> <p>Abscess: 4–10% (3 studies)</p> <p>Significant morbidity (requiring return to surgical intensive care unit, an invasive procedure or return to operating room): 5–36% (8 studies)</p> <p>Total morbidity (including minor complications): 45–60% (4 studies)</p> <p>In one study (Zanon), misperfusion of the chemotherapy agent occurred in 2 patients; 1 into the abdominal wall and 1 into the pleural cavity. Both were treated with early termination of HIIC.</p>	<p>Authors stated that ‘a meta-analysis was not appropriate due to the heterogeneity of patient populations and the different treatment regimens among the studies’.</p>

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## Studies included in Bijelic et al 2007

Study	N	Median follow up (months)	Median overall survival (months)	Median overall survival for optimal cytoreduction (months)	Median disease- / progression-free survival	2-year survival	3-year survival	5-year survival	% complete CRS	Impact of complete CRS on survival (p value)
Rufian (2006) <sup>22</sup>	33	NR	48 (mean)	66 (mean)	-	-	46% (patients with primary cancer)	37% (patients with primary cancer)	85%	<0.001
Hadi (2006) <sup>23</sup>	6	NR	-	-	-	67%	33%	-	88%	0.0001
Raspagliesi (2006) <sup>24</sup>	40	26.1	31.5 (mean)	-	10.5 (mean)	-	-	15%^	100%	NR
Reichman (2005) <sup>25</sup>	13	13.7	-	Not reached	15.4	-	55%	-	85%	0.03
Look (2004) <sup>26</sup>	28	26.9	45.8	55.9	17.3	60%	-	-	57%	0.037
Piso (2004) <sup>27</sup>	19	24	33 (mean)	-	-	-	-	15%	47%	Not significant
Zanon (2004) <sup>28</sup>	30	18.9 (mean)	28.1	37.8	-	60%	35%	12%	77%	NR
Ryu (2004) <sup>29</sup>	57	46.7 (mean)	-	-	-	-	-	63.4%	84%	0.003
Chatzigeorgiou (2003) <sup>30</sup>	20	NR	-	29	-	-	-	-	60%	<0.05
DeBree (2003) <sup>31</sup>	19	30 (mean)	54	-	26	71%	63%	42%	79%	-
Kecmanovic (2003) <sup>32</sup>	11	NR	22	-	-	-	-	-	NR	-
Van der Vange (2000) <sup>33</sup>	5	NR	-	-	-	-	-	-	100%	-
Fujimura (1999) <sup>34</sup>	6	NR	21.9	-	-	-	20%	-	NR	-
Kober (1996) <sup>35</sup>	12	9.2 (mean)	-	-	-	-	-	-	48%	0.09

CRS = cytoreduction surgery; NR = not reported

Abbreviations used: CRS / CS= cytoreduction surgery; EPIC = early postoperative intraperitoneal chemotherapy; HIIC = heated intraoperative intraperitoneal chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; IPCH = intraperitoneal chemotherapy; IPHC = intraperitoneal hyperthermic chemotherapy			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Verwaal et al (2008)<sup>2</sup></p> <p>Study type: <b>Prospective RCT</b></p> <p>Country: Netherlands</p> <p>Study period: 1998–2007 (patients assigned between Jan 1998 and Aug 2001)</p> <p>Study population: patients with histologically proven peritoneal metastases of colorectal adenocarcinoma or positive cytology of ascites, who were diagnosed either at first presentation or at recurrence of colorectal cancer and who were younger than 71 years and fit for major surgery. <b>n = 105 (54 vs. 51)</b></p> <p>Age: 54 years (median) (range 28–70 years)</p> <p>Sex: 55% male</p> <p>Primary cancer sites: colon (n = 75), appendix (n = 18), rectum (n = 12)</p> <p>Inclusion criteria: patients with evidence of distant metastases were excluded, as were patients who had received fluorouracil-based chemotherapy in the last 12 months (although they were allowed to enter the study after the first year).</p> <p>Technique: cytoreduction followed by HIPEC (mitomycin C) using the open coliseum approach (+ systemic chemotherapy started 6 weeks after operation) vs. standard systemic chemotherapy (5-FU leucovorin) given weekly for 26 weeks or until progression or unacceptable toxicity (any surgery conducted in this group was to relieve intestinal obstruction only).</p> <p>Follow-up: <b>8 years (median), range 72–115 months</b></p> <p>Conflict of interest: none reported</p>	<p><b>Disease-specific survival</b></p> <p>Experimental arm: 22.2 months</p> <p>Control arm: 12.6 months (p = 0.028)</p> <p><b>Progression-free survival:</b></p> <p>Experimental arm: 12.6 months</p> <p>Control arm: 7.7 months (p = 0.020)</p> <p>Median survival of 48 months in experimental arm.</p> <p>5-year survival of 45% for those who achieved complete cytoreduction (R-1) in experimental arm.</p>	<p><b>Experimental arm:</b></p> <p>2 patients died in intensive care within 40 days of operation due to uncontrollable abdominal sepsis.</p> <p>Another 2 patients died more than 3 months after the operation (1 abdominal sepsis and 1 massive lung embolism)</p> <p>No comparable figures are available for the standard care group</p> <p>Postoperative complications reported in experimental arm reported in Verwaal et al 2003<sup>21</sup>.</p> <ul style="list-style-type: none"> <li>• Renal obstruction = 4.2% (2/48)</li> <li>• Anuria = 6.2% (3/48)</li> <li>• Cardiac arrhythmia = 2.1% (1/48)</li> <li>• Heart failure = 12.5% (6/48)</li> <li>• Gastrointestinal fistula = 14.6% (7/48)</li> <li>• Pancreatitis = 2.1% (1/48)</li> <li>• Haemorrhage = 12.5% (6/48)</li> <li>• Psychological disorders = 10.4% (5/48)</li> <li>• Leukopenia = 16.7% (8/48)</li> <li>• Thrombocytopenia = 4.2% (2/48)</li> <li>• Neuropathy = 4.2% (2/48)</li> <li>• Pleural effusion = 2.1% (1/48)</li> <li>• Fever = 6.2% (3/48)</li> <li>• Pulmonary embolism within 3 months of surgery = 4.2% (2/48)</li> <li>• Pneumonia = 2.1% (1/48)</li> <li>• Catheter infections = 6.2% (3/48)</li> </ul> <p>Complications of control arm not stated</p>	<ul style="list-style-type: none"> <li>• This study reports extended follow-up of Verwaal 2003 which was reported in table 2 of the original overview.</li> <li>• Method of randomisation is unclear</li> <li>• Patient and tumour characteristics well balanced within both arms</li> <li>• Survival estimated by Kaplan–Meier method and tested following the intention-to-treat principle. However, not all patients completed planned treatment: <ul style="list-style-type: none"> <li>– Control arm: 8 patients never started systemic chemotherapy (rapid progression / withdrawn consent and 1 patient with pseudomyxoma); 43/51 (84%) completed the 6 weeks course.</li> <li>– HIPEC arm: 6 patients did not undergo procedure (1 died, 2 developed systemic metastases, 1 diagnosed with primary lung cancer and died within 3 months, 1 diagnosed with mesothelioma and 1 withdrew consent)</li> </ul> </li> <li>• During follow-up, 1 patient moved from the control arm to the experimental arm (patient had a recurrence after initial treatment completed)</li> <li>• Data for patients who crossed over or did not start treatment was censored at analysis.</li> <li>• Paper does not provide detail on how many patients were alive at the end of follow-up and how many were lost to follow-up.</li> </ul>

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<p>Glehen et al (2004)<sup>3</sup></p> <p><b>Study type: Retrospective non-randomised comparative study</b></p> <p>Country: International (28 institutions)</p> <p>Study period: May 1987 – Dec 2002</p> <p>Study population: patients with peritoneal carcinomatosis from colorectal origin confirmed by pathologic examination.</p> <p>n = <b>506 (271 vs. 123 vs. 112)</b></p> <p>Age: 51 years (median) (range 16–81 years)</p> <p>Sex: 233/506 = 46.1% male</p> <p>Primary cancer sites: right colon (39.5%), sigmoid (28.7%), left colon (12.5%), rectum (7.9%), transverse colon (7%), multiple locations (1.4%) and unknown (3%)</p> <p>Limited carcinomatosis: 171/506 (33.8%)</p> <p>Extensive carcinomatosis: 329/506 (65%)</p> <p>Unknown extent: 6/506 (1.2%)</p> <p>Inclusion criteria: appendiceal and extra-abdominal malignancies were excluded, as were cases where IPCH had been performed more than 7 days after surgery.</p> <p>Technique: CRS + IPCH (all intraoperative but mixture of open/closed approaches) vs. CRS + EPIC (delivered during 5 days after surgery) vs. CRS+ EPIC + IPCH</p> <p>Follow-up: <b>53 months (median), range 5–192 months</b></p> <p>Conflict of interest: None ('authors indicated no potential conflicts of interest')</p>	<p><b>Rate of complete cytoreduction:</b></p> <p>Complete (CCR-0): 271/506 (54%)</p> <p>&lt;5 mm (CCR-1): 106/506 (21%)</p> <p>&gt;5 mm(CCR-2): 129/506 (25%)</p> <p><b>Survival</b></p> <p>IPCH: 19.2 months (median)</p> <p>EPIC: 19.2 months (median)</p> <p>IPCH + EPIC: 21.6 months (median) (p = 0.61)</p>		<table border="1"> <thead> <tr> <th></th> <th>% survival 1 year</th> <th>% survival 3 year</th> <th>% survival 5 year</th> <th>Median survival (months)</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>72</td> <td>39</td> <td>19</td> <td>NR</td> </tr> <tr> <td>Disease free</td> <td>40</td> <td>16</td> <td>10</td> <td>NR</td> </tr> <tr> <td>CCR-0</td> <td>87</td> <td>47</td> <td>31</td> <td>32.4</td> </tr> <tr> <td>CCR-1</td> <td>79</td> <td>29</td> <td>15</td> <td>24</td> </tr> <tr> <td>CCR-2</td> <td>38</td> <td>6</td> <td>0</td> <td>8.4</td> </tr> </tbody> </table> <p>There was a significant difference in survival between CCR categories (p &lt; 0.001)</p> <p>Patients who received postoperative systemic chemotherapy = 25.2 months (median)</p> <p>Patients who did not receive postoperative systemic chemotherapy = 15.6 months (median) (p = 0.021)</p> <p>Patients who had a second procedure = 57.6 months (median)</p> <p>Patients who did not have a second procedure = 18 months (median) (p&lt;0.001)</p>			% survival 1 year	% survival 3 year	% survival 5 year	Median survival (months)	Overall	72	39	19	NR	Disease free	40	16	10	NR	CCR-0	87	47	31	32.4	CCR-1	79	29	15	24	CCR-2	38	6	0	8.4	<p>Postoperative death: 20/506 (4%) including 9 septic shock, 5 respiratory complications, 1 pulmonary embolus, 1 stroke, 1 peritonitis, 1 aplasia, 1 acute renal failure, and 1 unknown</p> <p>Digestive fistula was involved in 7 of the 20 deaths.</p> <p>Major complications : 116/506 22.9% included, digestive fistula: 42/506 (8.3%)</p> <p>Systemic sepsis: 10/506 (2%)</p> <p>Postoperative bleeding: 9/506 (1.8%)</p> <p>Intra-abdominal abscess: 9/506 (1.8%)</p> <p>Respiratory distress: 8/506 (1.6%)</p> <p>Pneumonia: 8/506 (1.6%)</p> <p>Urinary fistula: 5/506 (1%)</p> <p>Line sepsis: 5/506 (1%)</p> <p>Bowel obstruction: 5/506 (1%)</p> <p>Pulmonary embolism: 2/506 (0.4%)</p> <p>Peritonitis: 2/506 (0.4%)</p> <p>Hematological toxicity: 12/506 (2.4%)</p> <p>Other: 6/506 (1.2%)</p> <p>Reoperation was necessary in 54 patients (10.7%)</p> <p>Extensive carcinomatosis (relative risk [RR] 1.7, range 1.2–2.5, p = 0.005) and use of EPIC (RR 1.4, range 1.0–1.9, p = 0.032) both significantly increased risk of complications.</p>	<p>275/506 (54.3%) patients had previously been treated with systemic chemotherapy.</p> <p>Cytoreduction was conducted at the same time as resection of primary tumor in 99 patients (19.6%).</p> <p>204/506 (48.7%) of patients received additional systemic chemotherapy.</p> <p>26/506 (5%) had a second procedure.</p> <p>Survival: male 16.8 months vs. female 21.6 months (p = 0.003). Men diagnosed more often with extended carcinomatosis (p = 0.023, RR 1.16)</p> <p>Patients older than 65 years had a significantly lower survival rate than younger patients (p = 0.037)</p>
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IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

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<p><b>Survival</b></p> <table border="1"> <thead> <tr> <th></th> <th>% surviving 3 years (SE)</th> <th>% surviving 5 years (SE)</th> <th>Median survival in months (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Experimental</td> <td>26 (4.1)</td> <td>12.5 (3.4)</td> <td>16.5 (14.7–20.8)</td> </tr> <tr> <td>Control</td> <td>57.1 (5.3)</td> <td>33.9 (5.9)</td> <td>40.1 (34–58.3)</td> </tr> </tbody> </table> <p>SE: standard error</p>			% surviving 3 years (SE)	% surviving 5 years (SE)	Median survival in months (95% CI)	Experimental	26 (4.1)			12.5 (3.4)	16.5 (14.7–20.8)	Control	57.1 (5.3)	33.9 (5.9)	40.1 (34–58.3)	<table border="1"> <thead> <tr> <th>(figures are approximate as taken from a graph)</th> <th>Experimental group (%)</th> <th>Control group (%)</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Grade I (any minor deviation from normal postoperative course)</td> <td>2</td> <td>4</td> <td>NS</td> </tr> <tr> <td>Grade II (requiring pharmacological intervention)</td> <td>27</td> <td>7</td> <td>0.001</td> </tr> <tr> <td>Grade IIIa (No general anaesthetic)</td> <td>4</td> <td>11</td> <td>NS</td> </tr> <tr> <td>Grade IIIb (performed under general anaesthetic)</td> <td>4</td> <td>6</td> <td>NS</td> </tr> <tr> <td>Grade IVa (single organ dysfunction)</td> <td>0</td> <td>6</td> <td>NS</td> </tr> <tr> <td>Grade IVb (multi-organ dysfunction)</td> <td>6</td> <td>1</td> <td>NS</td> </tr> <tr> <td>Grade V (death)</td> <td>6</td> <td>4</td> <td>NS</td> </tr> </tbody> </table> <p>Grade II group included 9 patients who required growth factor support for neutropenia</p>		(figures are approximate as taken from a graph)	Experimental group (%)	Control group (%)	p value	Grade I (any minor deviation from normal postoperative course)	2	4	NS	Grade II (requiring pharmacological intervention)	27	7	0.001	Grade IIIa (No general anaesthetic)	4	11	NS	Grade IIIb (performed under general anaesthetic)	4	6	NS	Grade IVa (single organ dysfunction)	0	6	NS	Grade IVb (multi-organ dysfunction)	6	1	NS	Grade V (death)	6
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Study details	Key efficacy findings	Key safety findings	Comments
<p>Elias et al (2009)<sup>b</sup></p> <p>Study type: <b>Non-randomised comparative study</b></p> <p>Country: France</p> <p>Study period: Jan 1998 – Dec 2003</p> <p>Study population: Patients with gross peritoneal carcinomatosis from colorectal adenocarcinoma</p> <p>n = <b>96 (48 vs. 48)</b></p> <p>Age (mean): cases 46 years, controls 51 years (p = 0.01)</p> <p>Sex: cases 64% male, controls 66% male (p = 0.8)</p> <p>Inclusion criteria:</p> <p>Cases: no huge and symptomatic peritoneal carcinomatosis, no extra-abdominal malignancies, a good general status and younger than 66 years, no disease progression after 2–3 months of neoadjuvant chemotherapy.</p> <p>Comparison group: a good general status (World Health Organization performance status of 1 or 2), younger than 65 years old, no extra-abdominal extension, no evidence of bowel obstruction, no tumour larger than 2 cm on computed tomography scan and no rapid progression of peritoneal carcinomatosis under systemic chemotherapy.</p> <p>Technique: CS + HIPEC + systemic chemotherapy (cases: prospectively included) vs. palliative chemotherapy + some received palliative surgery (controls: retrospectively included)</p> <p>Follow-up:</p> <p><b>Cases: 63 months (median)</b></p> <p><b>Controls: 95.7 months (median)</b></p> <p>Conflict of interest: None ('authors indicated no potential conflicts of interest')</p>	<p><b>2-year survival:</b></p> <p>Cases: 81% (95% CI 68–90%)</p> <p>Controls: 65% (95% CI 55–74%)</p> <p><b>5-year survival:</b></p> <p>Cases: 51% (95% CI 36–65%)</p> <p>Controls: 13% (95% CI 6–26%)</p> <p>(p &lt; 0.05)</p> <p><b>Median survival:</b></p> <p>Cases: 62.7 months</p> <p>Controls: 23.9 months (p &lt; 0.05)</p>	<p>None reported</p>	<p>All patient characteristics were comparable except age and tumour differentiation (significantly more patients had well differentiated tumours in the cases group; p = 0.02)</p> <p>CRS was complete for all cases, with no residual peritoneal disease exceeding 1 mm.</p>

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Study details	Key efficacy findings	Key safety findings	Comments
<p>Sideris et al (2009)<sup>5</sup></p> <p>Study type: <b>Prospective non-randomised comparative study</b></p> <p>Country: Canada</p> <p>Study period: Jan 1998 – June 2005</p> <p>Study population: patients with peritoneal surface spread of appendiceal cancer treated at a tertiary care centre</p> <p>n = <b>37 (11 vs. 13 vs. 13)</b></p> <p>Age: 51 years (mean), range 33–73 years</p> <p>Sex: 17/37 (46%) male</p> <p>Inclusion criteria: diagnosis proven by histological examination, no evidence of visceral metastasis on computed tomography of chest and abdomen, technically resectable disease and good enough health status to tolerate major surgery.</p> <p>Technique: CRS + HIPEC using a closed approach and oxaliplatin (2002–2005) vs. CRS + normothermic EPIC for 5 days in immediate postoperative period (1998–2002) vs. incomplete cytoreduction (no intraperitoneal chemotherapy administered)</p> <p>Follow-up: <b>23 months (median), range 7–81 months</b></p> <p>Conflict of interest: None declared</p>	<p><b>5-year survival</b></p> <p>Overall: 56% (95% CI 34–77%)</p> <p>Overall for patients with a grade 1 tumour: 87% (95% CI 64–100%)</p> <p>All patients with grade 0 tumours survived and all patients with grade 2 tumours died within 5 years (p &lt; 0.001)</p> <p>HIPEC group: 60% (95% CI 10–100%)</p> <p>EPIC group: 58% (95% CI 30–86%)</p> <p>No significant difference between EPIC and HIPEC</p> <p>Survival not reported for incomplete cytoreduction group.</p>	<p>No mortality attributed to surgery.</p> <p>Overall complication rate: 36%</p> <p>Fistula: 16%(6/37)</p> <p>Intra-abdominal abscess: 12%</p> <p>Hemorrhage: 9%</p> <p>One patient in the HIPEC group experienced grade 2 neuropathy that lasted for 1 week after surgery and then grade 3 thrombocytopenia 1 week postoperatively.</p> <p>No significant difference in the complication rates between EPIC and HIPEC groups.</p> <p>Blood loss (ml): mean 876, standard deviation 654, median 755, range 100–3500.</p>	<p>One patient in the HIPEC group received mitomycin C instead of oxaliplatin.</p> <p>No patients were lost during follow-up.</p> <p>Authors reported in the discussion section that HIPEC is more comfortable for the patient and is simpler for nursing staff.</p>

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Study details	Key efficacy findings	Key safety findings	Comments
<p>Levine et al (2007)<sup>7</sup></p> <p>Study type: <b>Prospective case series</b></p> <p>Country: USA</p> <p>Study period: Dec 1991 – June 2006</p> <p>Study population: Patients with peritoneal surface malignancy</p> <p>n = <b>460</b></p> <p>Age: 53 years (mean), range 15–87 years</p> <p>Sex: 232/460 (49.6%) male</p> <p>Race: 406/460 (90.2%) Caucasian, 39/460 (8.7%) African–American and 15/460 (1.1%) other</p> <p>Primary origin of tumor: 1 adrenal (0.2%), 163 appendix (35.4%), 42 gastric (9.1%), 133 colorectal (28.9%), 3 gall bladder (0.7%), 9 gastrointestinal stromal (2%), 1 liver (0.2%), 27 mesothelioma (5.9%), 46 ovary (10%), 5 pancreas (1.1%), 11 sarcoma (2.4%) 6 small bowel (1.3%), 5 urachal (1.1%) and 8 unknown (1.7%)</p> <p>Inclusion criteria: normal organ function (serum creatinine &lt;2 mg/dl, alkaline phosphatase and serum aspartate transaminase or alanine transaminase less than 3 times the upper limit of normal, white blood cell count <math>\geq 4000/\text{mm}^3</math>, and platelet count <math>\geq 100,000/\text{mm}^3</math>).</p> <p>Technique: CRS + intraoperative IPHC using mitomycin C</p> <p>Follow-up: <b>55.4 months (median)</b></p> <p>Conflict of interest: None (portion of work supported by Robert Welborne Fund)</p>	<p>Median overall survival: 22.2 months</p> <p>1-year survival rate: 66.8%</p> <p>3-year survival rate: 40%</p> <p>5-year survival rate: 27.8%</p> <p>Median survival by site of origin:</p> <p>Appendix: 63.5 months</p> <p>Colorectal: 16.4 months</p> <p>Gastric: 6.1 months</p> <p>Mesothelioma: 27.1 months</p> <p>Ovary: 28.5 months</p> <p>Sarcoma: 28.1 months (p = 0.0001)</p> <p>Factors correlating with improved survival (multivariate analysis):</p> <p>Primary tumor site (p = 0.0001)</p> <p>Resection status (p = 0.001)</p> <p>Complications (p = 0.0006)</p>	<p>30-day mortality rate: 22/460 (4.8%)</p> <p>30-day morbidity rate: 43.1%</p> <p>Complication included wound infection, hematological toxicity, sepsis, respiratory failure, anastomotic leak, pneumonia and enterocutaneous fistula.</p> <p>Patients who experienced a complication had poorer survival than those who did not (p = 0.002)</p> <p>Complications were less common in patients undergoing R0/1 resections compared with patients with more residual disease (p = 0.044)</p>	<p>41 patients (8.9%) had a second IHPC procedure; 4 patents (0.9 %) had 3 procedures.</p> <p>Sodium thiosulphate was used as the chemotherapy agent for mesothelioma and cisplatinum or carboplatinum for ovarian cancer.</p>

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis



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Study details	Key efficacy findings					Comments		
<p>McQuellon et al (2007)<sup>8</sup></p> <p>Study type: <b>Prospective case series (quality of life study)</b></p> <p>Country: USA</p> <p>Study period: Jan 1998 – Jan 2005</p> <p>Study population: Patients with peritoneal carcinomatosis n = <b>96</b></p> <p>Age: 52.9 years (mean), range: 27–80 years</p> <p>Sex: 49/96 (51%) male</p> <p>Race: 86/96 (90%) Caucasian, 9/96 (9%) African–American and 1/96 (1%) other</p> <p>Primary origin of tumour: 36 appendix (38%), 24 colon/rectum (25%), 9 mesothelioma (9%), 5 ovary (5%), 4 stomach (4%) and 18 miscellaneous (19%).</p> <p>Inclusion criteria: same as Levine 2007. In addition, patients had to be English speaking, 18+ years of age, not pregnant, be able to comprehend the study procedure. Patients not eligible if they had uncontrolled or severe cardiovascular disease, active viral, bacterial or fungal infection, active peptic ulcer, uncontrolled diabetes, or severe pulmonary disease. Patients with parenchymal liver metastatic disease or lung metastases were excluded.</p>	<b>FACT-C (cancer-specific):</b> mean scores (SD)					<p>This is a subset of the patients included in the Levine 2007 study described in the previous table.</p> <p>Authors do not describe reasons for high level of drop out between baseline and 3 months. This could be due to death or because patients are too ill to complete the questionnaires and is a potential source of bias.</p> <p>Description of scales used: FACT-C: higher score indicates better quality of life. Four subscales measure physical, functional, social/family and emotional well-being. Includes 9 specific questions relating to colon cancer. FACT-G is the same set of questions without the colon-specific scores. The normal FACT-G score for the general US adult population is approximately 80.</p> <p>SF-36: Scores range from 0–100. Higher scores indicate better quality of life. Mean scores for the general population are general health (71.8), vitality (61.8), social functioning (84), role emotional (83.6), mental health (75.3) and bodily pain (73.1).</p>		
		Baseline (n = 96)	3 months (n = 38)	6 months (n = 32)	12 months (n = 24)		p value	
	Physical well-being	21.0 (6.1)	19.6 (6.0)	23.3 (4.2)	23.2 (3.7)		0.018	
	Social / family well-being	23.9 (4.1)	23.1 (3.7)	23.0 (3.9)	23.7 (3.9)		0.27	
	Emotional well-being	16.0 (5.1)	18.9 (3.4)	17.8 (4.0)	17.8 (4.0)		0.0001	
	Functional well-being	17.9 (5.7)	18.4 (5.5)	20.8 (5.6)	20.4 (4.9)		0.045	
	Total FACT-G score	78.9 (14.6)	80.0 (13.3)	84.9 (13.2)	85.5 (11.5)		0.017	
	Total FACT-C score	101.0 (18.2)	103.2 (17.1)	109.3 (16.0)	111.1 (13.1)		0.008	
	Indicates all areas except social/family well being significantly improved over a year. The total scores indicate a significant overall improvement in quality of life over a year.							
	<b>SF-36 (general health):</b> mean score (SD)							
	Baseline (n= 95)	3 months (n = 38)	6 months (n = 32)	12 months (n = 24)	p value			
Physical functioning	69.5 (27.5)	53.9 (37.8)	80.0 (17.4)	71.0 (25.0)	0.0006			
Role physical	36.3 (42.6)	24.3 (37.3)	54.0 (45.2)	53.0 (45.3)	0.016			
Bodily pain	64.8 (26.7)	62.9 (27.6)	82.8 (17.5)	81.5 (20.1)	0.0007			
General health	55.6 (15.6)	56.3 (16.4)	52.7 (14.5)	52.2 (10.6)	0.37			
Vitality	58.1 (10.4)	63.1 (13.9)	58.1 (10.6)	56.8 (7.3)	0.065			
Social functioning	51.2 (14.3)	51.5 (10.1)	56.4 (13.8)	44.0 (13.6)	0.055			
Role emotional	67.4 (42.1)	74.5 (35.8)	75.3 (38.5)	70.7 (41.7)	0.71			
Mental health	61.3 (9.6)	64.8 (7.9)	65.3 (8.0)	61.4 (6.7)	0.055			
Indicates physical functioning, problems with daily activities as a result of physical functioning and bodily pain significantly improved over a year.								

<p>McQuellon et al (2007) continued</p> <p>Technique: procedure same as Levine 2007. Patients were asked to complete a pack of questionnaires delivered by post at baseline (prior to surgery), 3 months, 6 months and 12 months. Questionnaires used:</p> <ul style="list-style-type: none"> <li>• The Functional Assessment of Cancer Therapy–Colon Scale (FACT-C)</li> <li>• The Medical Outcomes Study Health Survey, Short Form 36 (SF-36)</li> <li>• Brief Pain Inventory – Short Form (BPI)</li> <li>• The Center for Epidemiologic Studies–Depression Scale (CES-D)</li> <li>• The Eastern Cooperative Oncology Group (ECOG) Performance Status Rating Scale</li> </ul> <p>Follow-up: <b>12 months</b></p> <p>Conflict of interest: None (supported in part by the Robert Welborne Fund)</p>	<p><b>BPI (Pain)</b></p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>3 months</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>95</td> <td>37</td> </tr> <tr> <td>% scoring 1–3 on scale (low level of pain)</td> <td>54</td> <td>57</td> </tr> <tr> <td>% scoring 8–10 on scale (high level of pain)</td> <td>17 (16/95)</td> <td>8 (3/37)</td> </tr> </tbody> </table> <p>Indicates reduction in % of patients in severe pain after 3 months (although use of pain medication is not reported)</p> <p><b>CES-D (Depression)</b></p> <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>3 months</th> <th>6 months</th> <th>12 months</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>95</td> <td>39</td> <td>32</td> <td>26</td> </tr> <tr> <td>Mean (SD)</td> <td>13.8 (9.6)</td> <td>11.5 (7.8)</td> <td>10.3 (7.4)</td> <td>10.6 (9.1)</td> </tr> <tr> <td>% scoring &gt;=17</td> <td>32</td> <td>19</td> <td>24</td> <td>24</td> </tr> </tbody> </table> <p>Significant drop in depression over 1 year (p = 0.024)</p> <p><b>ECOG Performance status (cancer-specific)</b></p> <table border="1"> <thead> <tr> <th></th> <th>Baseline (n = 95)</th> <th>3 months (n = 38)</th> <th>6 months (n = 32)</th> <th>12 months (n = 24)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>54 (57%)</td> <td>8 (23%)</td> <td>17 (53%)</td> <td>14 (58%)</td> </tr> <tr> <td>1</td> <td>23 (24%)</td> <td>20 (51%)</td> <td>13 (44%)</td> <td>8 (33%)</td> </tr> <tr> <td>2</td> <td>12 (13%)</td> <td>8 (21%)</td> <td>1 (3%)</td> <td>2 (9%)</td> </tr> <tr> <td>3</td> <td>6 (6%)</td> <td>2 (5%)</td> <td>0</td> <td>0</td> </tr> <tr> <td>4</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> </tbody> </table> <p>Indicates reduction in % patients requiring best rest for &gt;50% of waking day and an increase in % patients who are fully ambulatory with symptoms.</p> <p>Question: Compared to 1 year ago, how would you rate your health in general now?</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline (n = 95)</th> <th>3 months (n = 33)</th> <th>6 months (n = 31)</th> <th>12 months (n = 24)</th> </tr> </thead> <tbody> <tr> <td>Much better / somewhat better</td> <td>19 (20%)</td> <td>14 (42%)</td> <td>18 (58%)</td> <td>16 (66%)</td> </tr> <tr> <td>Same</td> <td>23 (24%)</td> <td>4 (12%)</td> <td>5 (16%)</td> <td>4 (17%)</td> </tr> <tr> <td>Somewhat worse / much worse</td> <td>53 (56%)</td> <td>15 (46%)</td> <td>8 (26%)</td> <td>4 (17%)</td> </tr> </tbody> </table>		Baseline	3 months	N	95	37	% scoring 1–3 on scale (low level of pain)	54	57	% scoring 8–10 on scale (high level of pain)	17 (16/95)	8 (3/37)		Baseline	3 months	6 months	12 months	N	95	39	32	26	Mean (SD)	13.8 (9.6)	11.5 (7.8)	10.3 (7.4)	10.6 (9.1)	% scoring >=17	32	19	24	24		Baseline (n = 95)	3 months (n = 38)	6 months (n = 32)	12 months (n = 24)	0	54 (57%)	8 (23%)	17 (53%)	14 (58%)	1	23 (24%)	20 (51%)	13 (44%)	8 (33%)	2	12 (13%)	8 (21%)	1 (3%)	2 (9%)	3	6 (6%)	2 (5%)	0	0	4	0	0	0	0		Baseline (n = 95)	3 months (n = 33)	6 months (n = 31)	12 months (n = 24)	Much better / somewhat better	19 (20%)	14 (42%)	18 (58%)	16 (66%)	Same	23 (24%)	4 (12%)	5 (16%)	4 (17%)	Somewhat worse / much worse	53 (56%)	15 (46%)	8 (26%)	4 (17%)	<p>Description of scales used:</p> <p>BPI: measures intensity and interference of pain in the patient's life. Pain scale 0–10 (0 = no pain and 10 = worst pain)</p> <p>CES-D: score of &gt;=17 indicates significant depressive symptoms.</p> <p>ECOG: Rates activity level. 0 = fully ambulatory, no symptoms; 1 = fully ambulatory with symptoms; 2 = require bed rest &lt;50% of waking day; 3 = require bed rest &gt;50% waking day; 4 = bedridden.</p>
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Abbreviations used: CRS / CS= cytoreduction surgery; EPIC = early postoperative intraperitoneal chemotherapy; HIIC = heated intraoperative intraperitoneal chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; IPCH = intraperitoneal chemotherapy; IPHC = intraperitoneal hyperthermic chemotherapy		
Study details	Key safety findings (This table describes serious safety outcomes taken from smaller case series that have not occurred in the previous 8 studies in table 2)	Comments
<p>Muller et al (2008)<sup>9</sup>  Glehen et al (2003)<sup>10</sup>  Stephens et al (1999)<sup>13</sup>  Glehen et al (2004)<sup>11</sup>  Glehen et al (2006)<sup>12</sup>  Yan et al (2007)<sup>14</sup>  Gusani et al (2008)<sup>15</sup>  Elias et al (2007)<sup>16</sup>  Moran et al (2006)<sup>17</sup>  Culliford et al (2001)<sup>18</sup>  Lanuke et al (2009)<sup>19</sup>  Roviello et al (2006)<sup>20</sup></p>	<p><b>Muller 2008</b>  Case series of 241 patients. Complication and mortality rate by year: 2003: 26.5% and 2%, 2004: 20% and 0%, 2005: 14% and 1%. Complications include: acute respiratory distress syndrome: 1, arrhythmia: 2, thrombosis: 2, pancreatitis: 1 prolonged paralysis: 3</p> <p><b>Glehen 2003</b>  Case series of 207 patients. Postoperative mortality = 3%. Postoperative morbidity = 24%.  Complications include: DVT: 1.8% (4), pulmonary embolism: 1.3% (3), myocardial necrosis: 0.4% (1)</p> <p><b>Stephens 1999</b>  Case series of 200 patients. Treatment related mortality = 1.5%. Grade 3/4 morbidity = 27%.  Complications include: Pneumothorax: 2.5% (5), DVT: 1% (2) and pulmonary embolism: 0.5% (1)</p> <p><b>Glehen 2004</b>  Case series of 174 patients. Mortality: 0%, morbidity: 33.3%, Median survival: 20.5 months, 5-year survival: 15%.  Complications include: Pulmonary embolism: 5.8% (4) and pneumothorax: 2% (3)</p> <p><b>Glehen 2006</b>  Case series of 96 patients. 4-year survival for R0/R1 patients: 45%  Complications include: grade 3 neutropenia: 3.1% (3)</p> <p><b>Yan 2007</b>  Case series of 140 patients: Hospital mortality: 4%, severe morbidity: 20%, moderate morbidity: 44%  Complications include : pneumothorax 7% (10), chemotherapy-related neutropenia: 4% (5) and acute renal failure requiring dialysis in intensive care 1% (1).</p> <p><b>Gusani 2008</b>  Case series of 122 patients. 30-day mortality: 1.6%, appendiceal cancer 2-year survival: 66.7%, colorectal cancer 2-year survival: 36.7%. Complications include: pulmonary embolism: 3, haemolytic-uremic syndrome: 1, myocardial infarction: 1</p> <p><b>Elias 2007</b>  Case series of 106 patients. Postoperative mortality: 4% and morbidity: 66%. Complications include: grade 4 thrombocytopenia or neutropenia: 11%</p> <p><b>Moran 2006</b>  Case series of 100 patients. Postoperative mortality: 8% Complications include: DVT: 5, pulmonary embolism: 4 (fatal in 2)</p> <p><b>Culliford 2001</b>  Case series of 64 patients. Median survival: 34 months, 5-year survival: 28%. Complications include: pneumothorax: 1, DVT: 2 and pulmonary embolus: 1</p> <p><b>Lanuke 2009</b>  Case series of 60 patients. Complications include: VTE 10% (6/60)</p> <p><b>Roviello 2006</b>  Case series of 59 patients. Major morbidity: 27.9%, Reoperation required: 8.2%. Complications include: acute renal failure: 2, arrhythmias: 2</p>	

### ***Validity and generalisability of the studies***

- Studies included report on patients with peritoneal carcinomatosis resulting from a mixture of different primary cancers. It is unclear if the results can be generalised across different types of cancer.
- Only one RCT was available within the published literature. For this study, the method of randomisation is not clearly described and the number of patients was small.
- Comparability of groups in the non-randomised comparative trials may be questioned.
- A variety of chemotherapy agents, doses and temperatures were used when administering HIPEC (not reported in the tables due to lack of space), and it is unclear how this affects outcomes.
- Only one paper defined the time period in which postoperative deaths occurred.

### **Specialist Advisers' opinions**

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Professor Matthew Seymour (National Cancer Research Institute, Colorectal Clinical Studies Group), Mr Brendan Moran (Association of Coloproctology of Great Britain and Ireland), Miss Sarah O'Dwyer (British Association of Surgical Oncology (BASO) and Association of Coloproctology of Great Britain and Ireland), Mr Irving Taylor, Mr Setty Viswanath, Mr Colin Johnson and Mr Sami Shimi (Association of Upper Gastrointestinal Surgeons for Great Britain and Ireland (AUGIS)):

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- Two of the Specialist Advisers perform this procedure regularly (one is Director of a national centre for the management of pseudomyxoma peritonei of appendiceal origin funded by the National Commissioning Group (NCG)). Three of the other Specialist Advisers have never performed this procedure but have taken part in patient selection or referred a patient for this procedure at least once.
- One Specialist Adviser considers the procedure to be reasonably well established for pseudomyxoma peritonei but less well established and more controversial as a treatment for peritoneal carcinomatosis.
- Three Specialist Advisers consider the procedure to be novel and of uncertain safety and efficacy. One Adviser stated that this is established practice and no longer new.
- Five Specialist Advisers agreed that there are fewer than 10% of specialists engaged in this area of work.
- Three Specialist Advisers reported that the standard comparator for this procedure is palliative chemotherapy. Other comparators include additional palliative surgical resection for symptom relief, best supportive care and paracentesis.
- Key efficacy outcomes: overall survival, 2-, 3- and 5-year survival, 30-day surgical mortality, disease-free survival, survival time with good quality of life, stoma-free survival, palliation of symptoms such as pain or ascites, recurrence rate, treatment-related morbidity, return to work, return to recreational activities and return to sexual functioning.
- Adverse events: significant risk of postoperative death, bleeding, major morbidity (e.g. perforation, fistula, infection, thrombosis, sepsis), adverse symptoms (e.g. abdominal pain, eating disturbances), chemotherapy-associated complications (e.g. neutropenia (<10%), renal failure (<5%), ureteric injury, liver failure (<5%) and bile duct injury (<1%)), hepatic dysfunction, vascular injury, anaemia, neuropathy, anaphylaxis, early recurrence and bowel obstruction.

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- One Specialist Adviser noted that the relatively high dose of mitomycin is a theoretical risk and post-procedural neutropenia is common which implies significant systemic absorption. However, another Adviser reported that this outcome is very uncommon at the dose that most people use.
- One Specialist Adviser noted that a single high-dose of mitomycin C could theoretically compromise the ability to receive palliative cytotoxic chemotherapy after relapse.
- One Specialist Adviser reported that he had seen one case of significant post-procedural hepatitis in a pseudomyxoma patient, most probably due to mitomycin C.
- One Specialist Adviser noted that there is potential for negative psychological impact and reduction in quality of life.
- One Specialist Adviser noted there is an individual and institutional learning curve. Currently, non-invasive imaging is very limited in its ability to assess the suitability for complete macroscopic tumour removal. The best results follow complete macroscopic tumour removal with localised peritoneal carcinomatosis (but this can only be established at laparotomy).
- Facilities required include specialised surgery, anaesthetics, critical care, oncology and pharmacy expertise to deliver HIPEC. Training is required in cytoreduction for different cancers, operating the perfusion machine, connecting the perfusion tubing and fluids, management of spillage of cytotoxic agents and safe disposal of tubing.
- One Specialist Adviser stated that selection of patients for the procedure is critical and that the procedure should be done as part of an RCT.
- One Specialist Adviser reports that there is a French multi-institutional registry of 1290 patients undergoing CRS and intraperitoneal chemotherapy for peritoneal carcinomatosis, which has been submitted for publication.

## **Patient Commentators' opinions**

NICE's Patient and Public Involvement Programme were unable to obtain patient commentary for this procedure.

## **Issues for consideration by IPAC**

- Should recommendations be made for specific types of peritoneal carcinomatosis depending on site of primary cancer (e.g. ovarian, colorectal, appendiceal)?
- Future study: a phase III RCT for stage III ovarian carcinoma comparing secondary debulking surgery with or without hyperthermic intraperitoneal chemotherapy is currently recruiting at the Netherlands Cancer Institute (NCT00426257). Estimated enrollment of 280 patients. The trial started in February 2007 with a planned completion date of January 2011. It is unclear from the protocol description if the chemotherapy is intraoperative.

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## Appendix A: Additional papers on cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Verwaal VJ, van RS, de BE et al. (2003) Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. <i>Journal of Clinical Oncology</i> 21:3737-3743.	RCT  n = 105 (51 vs. 54)  Follow-up: 21.6 months (median)  colon (n = 75), appendix (n = 18), rectum (n = 12)	Median survival 22.3 months in experimental arm and 12.6 months in the control arm. Treatment related mortality in experimental arm: 8%	Larger studies included in table 2  [In table 2 in original overview. Superseded by Verwaal 2008]
Bonvalot S, Cavalcanti A, Le PC et al. (2005) Randomized trial of cytoreduction followed by intraperitoneal chemotherapy versus cytoreduction alone in patients with peritoneal sarcomatosis. <i>European Journal of Surgical Oncology</i> 31:917-923.	RCT  n = 38 (19 vs. 19)  Follow-up: 60 months (median)  sarcomatosis	Overall survival similar in both groups (29 months)	Larger studies included in table 2
Fujimoto S, Takahashi M, Mutou T et al. (1997) Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. <i>Cancer</i> 79: 884-91.	Non-randomised comparative study  n = 68 (48 vs. 18)  Follow-up: NR  Stomach	5-year survival rate of IHCP patients was 41.6%. 50% survival duration of control group was 110 days.	Larger studies included in table 2  [In table 2 in original overview]
Elias D, Blot F, El Otmamy A et al. (2001) Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. <i>Cancer</i> 92: 71-6.	Non-randomised comparative study  n = 64 (37 vs.27)  Follow-up: 51.6 months (median)  colon (n = 46), rectum (n = 9), appendix (n = 9)	Postoperative mortality: 9.3% Postoperative morbidity: 54.6%  Overall 5-year survival: 27.4% Disease-free 5-year survival: 18.4% significantly better when metastasis free (p = 0.04)	Larger studies included in table 2  [In table 2 in original overview]

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Elias D, Benizri E, Di PD et al. (2007) Comparison of two kinds of intraperitoneal chemotherapy following complete cytoreductive surgery of colorectal peritoneal carcinomatosis [see comment]. Annals of Surgical Oncology 14:509-514.	non randomised comparative study n = 46 (23 vs. 23) Follow-up: 113 months (median) colorectal	5 year survival, mortality and morbidity not significantly different between 2 groups. Rate of digestive fistula higher in EPIC group (26%) compared to 0% in IPCH group (p=0.02)	Larger studies included in table 2
Hirose K, Katayama K, Iida A et al. (1999) Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. Oncology 57:106-14.	non randomised comparative study n = 37 (17 vs. 20) Follow-up: 5 years gastric	Peritoneal occurrence significantly less frequent and 5 year survival significantly higher in CHPP group compared to control.	Larger studies included in table 2
Sugarbaker PH, Chang D. (1999) Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Annals of Surgical Oncology 6:727-31.	Case series n = 385 Follow-up: 37.6 months (mean) appendix	Mortality: 2.7%, morbidity: 27%. Patients with complete cytoreduction and adenomucinosis 5-year survival: 86%. Incomplete cytoreduction 5-year survival: 20% Complications: pancreatitis 7.1%, fistula 4.7%	Larger studies included in table 2
Gomez PA, Barrios P, Rufian S et al. (2006) Management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy. European Journal of Surgical Oncology 32:628-631.	Case series n = 266 Follow-up: NR 93 ovary, 65 appendix, 51 colon, 27 mesothelioma, 20 gastric, 6 uterus and 4 sarcomatosis	Mortality: 7.8% Morbidity: 37.5% Median survival: 13.7months.	Larger studies included in table 2

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Kusamura S, Baratti D, Antonucci A et al. (2007) Incidence of postoperative pancreatic fistula and hyperamylasemia after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. <i>Annals of Surgical Oncology</i> 14:3443-3452.	Case series n = 265 Follow-up: NR 67 mesothelioma, 83 pseudomyxoma peritonei, 44 ovarian, 35 abdominal sarcomatosis, 15 colon, 12 gastric, 9 other	Postoperative pancreatic fistula: 13 cases (4.8%)	Larger studies included in table 2
Kusamura S, Baratti D, Younan R et al. (2007) Impact of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on systemic toxicity [see comment]. <i>Annals of Surgical Oncology</i> 14:2550-2558.	Case series n = 242 Follow-up: NR 62 mesothelioma, 74 pseudomyxoma peritonei, 40 ovarian, 33 abdominal sarcomatosis, 14 colon, 10 gastric, 9 other	Procedure related mortality: 1.2% G3-5 systemic toxicity rate: 11.7% (including bone marrow suppression: 13, nephrotoxicity: 14, neutropenic infection: 2, pulmonary toxicity: 1)  Multivariate analysis: does of cisplatin of 240 mg or more is a significant risk for G3-5 toxicity (odds ratio 2.78, 95% CI 1.2–6.45)	Larger studies included in table 2
Muller H, Hahn M, Weller L et al. (2008) Strategies to reduce perioperative morbidity in cytoreductive surgery. <i>Hepato-Gastroenterology</i> 55:1523-1529.	Case series n = 241 Follow-up: NR 14 appendix, 56 colorectal, 20 gastric, 10 mesothelioma, 99 ovarian, 3 fallopian tube, 2 peritoneum, 5 pseudomyxoma peritonei, 21 sarcoma of different origin and 11 small bowel/urachus	Complication and mortality rate by year:  2003: 26.5% and 2% 2004: 20% and 0% 2005: 14% and 1% 2006: 10% and 0%  Complications include: ARDS: 1 Arrhythmia: 2 Thrombosis: 2 Pancreatitis: 1 Prolonged paralysis: 3	Larger studies included in table 2

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Glehen O, Osinsky D, Cotte E et al. (2003) Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. <i>Annals of Surgical Oncology</i> 10:863–9.	Case series n = 207 Follow-up:NR	Postoperative mortality = 3%. Postoperative morbidity = 24%. No efficacy data.  Complications include: DVT: 1.8% (4) Pulmonary embolism: 1.3% (3) Myocardial necrosis: 0.4% (1)	Larger studies included in table 2  Larger studies included in table 2 Included in Appendix A in original overview  Results for different treatment regimens combined.
Kusamura S, Younan R, Baratti D et al. (2006) Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. <i>Cancer</i> 106:1144-1153	Case series n = 205 Follow-up: NR  50 mesothelioma, 49 pseudomyxoma peritonei, 41 ovarian, 32 abdominal sarcomatosis, 13 colon, 12 gastric and 8 other.	Major morbidity: 12% Operative mortality rate: 0.9% 10 patients presented with grade 3 and 4 toxicity.	Larger studies included in table 2
Stephens AD, Alderman R, Chang D et al. (1999) Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the Coliseum technique. <i>Annals of Surgical Oncology</i> 6:790–6.	Case series n = 200  Follow-up: 21.8 months (median)  Includes patients with pseudomyxoma peritonei.	Treatment related mortality = 1.5%. Grade 3/4 morbidity = 27%.  Complications include: Pneumothorax: 2.5% (5) DVT: 1% (2) Pulmonary embolism: 0.5% (1)	Larger studies included in table 2  [Included in Appendix A in original overview]

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
<p>Sugarbaker PH ,Jablonski KA. (1995) Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Annals of Surgery 221:124-132.</p>	<p>Case series n = 181 Follow-up: 24 months (mean) 130 appendiceal 51 colorectal</p>	<p>3-year survival for patients with grade 1 histology, no lymph node metastases and complete cytoreduction (n = 76): 99%</p> <p>3-year survival for patients with grade 2–3 histology, no metastases and complete cytoreduction (n = 23): 65%</p> <p>3-year survival for patients with any histology + lymph node metastases and complete cytoreduction (n = 24): 66%</p> <p>3-year survival for patients with incomplete cytoreductions: 20%</p>	<p>Larger studies included in table 2</p>
<p>Glehen O, Mohamed F, and Sugarbaker PH. (2004) Incomplete cytoreduction in 174 patients with peritoneal carcinomatosis from appendiceal malignancy. Annals of Surgery 240:278-285.</p>	<p>Case series n = 174 Follow-up: 5 years appendix</p>	<p>Mortality: 0% Morbidity: 33.3% Median survival: 20.5 months 5-year survival: 15% Complications include: Pulmonary embolism: 5.8% (4) Pneumothorax: 4.3% (3)</p>	<p>Larger studies included in table 2</p>
<p>Glehen O, Cotte E, Lifante JC et al. (2006) Peritoneal carcinomatosis in digestive cancers: cytoreductive surgery combined with intraperitoneal chemohyperthermia. The experience in Centre Hospitalier et Universitaire Lyon Sud (CHLS). Acta Chirurgica Belgica 106:285-290.</p>	<p>2 case series n = 145 (96+49) Follow-up: 99 months (median) colorectal + gastric cancer</p>	<p>First case series: 4 year survival for R0/R1 patients (n = 96): 45% Complications include: grade 3 neutropenia: 3.1% (3)</p> <p>Second case series: Median survival: 10 months</p>	<p>Larger studies included in table 2</p>

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis



Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
<p>Yan TD, Links M, Fransi S et al. (2007) Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy--a journey to becoming a Nationally Funded Peritonectomy Center. <i>Annals of Surgical Oncology</i> 14:2270-2280.</p>	<p>Case series</p> <p>n = 140</p> <p>Follow-up: 16 months (median) range: 2-117 months</p> <p>69 pseudomyxoma peritonei, 40 colorectal, 15 mesothelioma and 16 other</p>	<p>Hospital mortality: 4%, severe morbidity: 20% moderate morbidity: 44%</p> <p>Complications include: pneumothorax 7% (10), chemotherapy related neutropenia: 4% (5), acute renal failure requiring dialysis in intensive care 1% (1)</p>	<p>Larger studies included in table 2</p>
<p>Gusani NJ, Cho SW, Colovos C et al. (2008) Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. <i>Annals of Surgical Oncology</i> 15:754-763</p>	<p>Case series</p> <p>n = 122</p> <p>Follow-up: 35.9 months (median)</p> <p>47 appendiceal, 17 diffuse peritoneal adenomucinosis, 2 PMCA/ID, 28 PMCA, 28 colorectal, 16 ovarien, 15 msothelioma, 6 sarcoma, 2 gastric, 2 oesophageal, 1 cholangiocarcinoma, 1 gall bladder, 1 breast, 1 endometrial and 2 unknown (some patients fit more than one category)</p>	<p>30-day mortality: 1.6%</p> <p>Appendiceal cancer 2-year survival: 66.7%</p> <p>Colorectal cancer 2-year survival: 36.7%</p> <p>Complications include: pulmonary embolism: 3, haemolytic-uraemic syndrome: 1, myocardial infarction: 1</p>	<p>Larger studies included in table 2</p>

Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Cavaliere F, Valle M, De SM et al. (2006) 120 peritoneal carcinomatoses from colorectal cancer treated with peritonectomy and intra-abdominal chemohyperthermia: a S.I.T.I.L.O. multicentric study. In Vivo 20:747-750	Case series n = 120 Follow-up: NR colorectal	Major morbidity: 22.5% Mortality: 3.3% 3-year survival: 25.8%	Larger studies included in table 2
Verwaal VJ, van RS, Witkamp A et al. (2005) Long-term survival of peritoneal carcinomatosis of colorectal origin. Annals of Surgical Oncology 12:65-71	Case series n = 117 Follow-up: 46 months (median) colorectal	Median survival: 21.8 months 5-year survival: 19%	Larger studies included in table 2
Shen P, Levine EA, Hall J et al. (2003) Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. Archives of Surgery 138:26–33.	Case series n = 109 Follow-up: 52 months (median) colorectal (n = 40), appendix (n = 23), stomach (n = 19), peritoneum (n = 8), ovary (n = 6), retroperitoneum (n = 4), other (n = 4), unknown (n = 5)	3-year survival: 33% Median survival: 16 months	Larger studies included in table 2  [Included in table 2 in original overview]
Verwaal VJ and Zoetmulder FA. (2004) Follow-up of patients treated with cytoreduction and chemotherapy for peritoneal carcinomatosis of colorectal origin. European Journal of Surgical Oncology 30:280-285	Case series n = 107 Follow-up: 51 months (median) 15 appendix, 87 colon and 5 rectum	Recurrence in 63 patients out of 74 with effective initial treatment.	Larger studies included in table 2
Yonemura Y, Kawamura T, Bandou E et al. (2005) Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. British Journal of Surgery 92:370-375	Case series n = 107 Follow-up: 46 months (median) gastric	Operative mortality rate: 2.8% Median survival: 11.5 months 5 year survival: 6.7%	Larger studies included in table 2

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Elias D, Goere D, Blot F et al. (2007) Optimization of hyperthermic intraperitoneal chemotherapy with oxaliplatin plus irinotecan at 43 degrees C after complete cytoreductive surgery: mortality and morbidity in 106 consecutive patients. <i>Annals of Surgical Oncology</i> 14:1818-1824	Case series n = 106 Follow-up: NR 37 colon, 6 rectum, 5 appendix, 41 pseudomyxoma, 11 mesothelioma, 5 endocrine, 1 hepatocellular	Postoperative mortality: 4% and morbidity: 66% Complications include: grade 4 thrombocytopenia or neutropenia; 11%	Larger studies included in table 2
Verwaal VJ, Boot H, Aleman BMP et al. (2004) Recurrences after peritoneal carcinomatosis of colorectal origin treated with cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome. <i>Annals of Surgical Oncology</i> 11:375-9.	Case series n = 106 Follow-up: 47.5 months (median) colon (n = 82), appendix (n = 15), rectum (n = 5), unknown (n = 4)	Median survival: 10.3 months	Larger studies included in table 2  [Included in table 2 in original overview]
Verwaal VJ, van TH, van RS et al. (2004) Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated with aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. <i>British Journal of Surgery</i> 91:739-746	Case series n = 102 Follow-up: 41.6 months (median) colorectal	Median survival: 19.9 months. Location of tumour in rectum, poor differentiation and signet cell histological type were associated with shorter survival.	Larger studies included in table 2
Verwaal VJ, Tinteren HV, Ruth SV et al. (2004) Toxicity of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. <i>Journal of Surgical Oncology</i> 85: 61-7.	Case series n = 102 Follow-up: NR	Treatment related mortality = 8%. Surgical complications = 35%. Grade 3 toxicity and above = 65%.	Larger studies included in table 2  [Included in Appendix A in original overview]
Lanuke K, Mack LA, and Temple WJ. (2009) Phase II study of regional treatment for peritoneal carcinomatosis. <i>American Journal of Surgery</i> 197:614-618	Case series n = 101 Follow-up: 16 months (median) 55 appendix, 31 colon/rectum, 5 mesothelioma, 4 peritoneum, 3 small bowel, 2 ovary and 1 stomach	Perioperative mortality: 4% Grade 3 or 4 morbidity: 39%	Larger studies included in table 2

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Moran BJ, Mukherjee A, and Sexton R. (2006) Operability and early outcome in 100 consecutive laparotomies for peritoneal malignancy. British Journal of Surgery 93:100-104	Case series n = 100 Follow-up: NR 85 appendix, 4 mesothelioma, 4 colon, 3 ovarian and 4 miscellaneous	Postoperative mortality: 8% Complications include: DVT: 5, pulmonary embolism: 4 (fatal in 2)	Larger studies included in table 2
Fujimura T, Yonemura Y, Kawamura T et al. (1996) Cytoreductive surgery and sandwich therapy with chemohyperthermic peritoneal perfusion and intra-aortic chemotherapy for peritoneal dissemination in gastric cancer. Oncology Reports 3:513–7.	Case series n = 96 Follow-up: NR	Cytoreduction resection and/or chemo-hyperthermic peritoneal perfusion improves survival.	Larger studies included in table 2  [Included in Appendix A in original overview]  Includes patients with different treatment regimens.
Loggie BW, Fleming RA, McQuellon RP et al. (2000) Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. The American Surgeon 66:561–8.	Case series n = 84 Follow-up: 27 months (median)	Overall median survival 14.3 months. 1-year survival: 59%. Complications include: pulmonary embolism:4.	Larger studies included in table 2  [Included in Appendix A in original overview]  Patients also likely to be included in Shen et al, 2003
Beaujard AC, Glehen O, Caillot JL et al. (2000) Intraperitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. Cancer 88:2512-2519.	Case series n = 83 Follow-up: NR Digestive tract	3-year survival: Resectable gastric cancer: 80% Stage 1 carcinomatosis: 61% Stage II: 41% 1 year survival fro stage 3 and 4: 10%	Larger studies included in table 2
Elias D, Raynard B, Boige V et al. (2005) Impact of the extent and duration of cytoreductive surgery on postoperative hematological toxicity after intraperitoneal chemohyperthermia for peritoneal carcinomatosis. Journal of Surgical Oncology 90:220-225	Case series n = 83 Follow-up: NR 44 colorectal, 25 pseudomyxoma, 10 mesothelioma and 4 endocrine	Severe postoperative aplasia: 48% (40/83)	Larger studies included in table 2

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Yan TD, Zappa L, Edwards G et al. (2007) Perioperative outcomes of cytoreductive surgery and perioperative intraperitoneal chemotherapy for non-appendiceal peritoneal carcinomatosis from a prospective database [see comment]. Journal of Surgical Oncology 96:102-112	Case series n = 80 Follow-up: NR 47 colorectal, 20 ovarian, 5 sarcoma, 4 gastric and 4 small bowel	Postoperative mortality: 1.3% (1) Grade 3 adverse events: 45% (36)	Larger studies included in table 2
Shen P, Hawksworth J, Lovato J et al. (2004) Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma.[see comment]. Annals of Surgical Oncology 11:178-186	Case series n = 77 Follow-up: 15 months (median) colon (n = 74), rectum (n = 3)	Perioperative mortality: 12% Perioperative morbidity: 30% 5 year survival following complete resection: 34%	Larger studies included in table 2  [Included in table 2 in original overview]
Pestieau SR, Sugarbaker PH. (2000) Treatment of primary colon cancer with peritoneal carcinomatosis. Comparison of concomitant vs delayed management. Diseases of the Colon & Rectum 43:1341–8.	Case series n = 77 Follow-up: NR	Extent of cancer in abdomen and pelvis at the time of treatment correlated directly with survival.	Larger studies included in table 2  [Included in Appendix A in original overview]  Compares patients treated at different times after primary cancer.
Bijelic L, Yan TD, and Sugarbaker PH. (2007) Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. Annals of Surgical Oncology 14:2281-2288.	Case series n = 70 Follow-up: 40.8 months (mean) colorectal	49 had recurrent disease, median survival for this group: 30 months.	Larger studies included in table 2
Schmidt U, Dahlke MH, Klempnauer J et al. (2005) Perioperative morbidity and quality of life in long-term survivors following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. European Journal of Surgical Oncology 31:53-58	Case series n = 67 Follow-up: NR 22 appendix, 15 ovary, 7 colon, 4 peritoneum, 3 stomach, 3 pancreas, 3 liver, 3 small bowel, 2 retroperitoneal sarcoma, 1 uterus and 3 unknown	Morbidity: 34% Postoperative mortality: 4.5%  Quality of life: Mean global health score: 62.6 (compared with 73.3 in control group). Functional status and social functioning were both impaired	Larger studies included in table 2

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Culliford AT 4th, Brooks AD, Sharma S et al. (2001) Surgical debulking and intraperitoneal chemotherapy for established peritoneal metastases from colon and appendix cancer. <i>Annals of Surgical Oncology</i> 8:787-95.	Case series n = 64  Follow-up: 17 months (median) range: 0–132 months  47 colon and 17 appendix	Median survival: 34 months 5-year survival: 28%  Complications include: pneumothorax: 1, DVT: 2 and pulmonary embolus: 1	Larger studies included in table 2
Lanuke K, Mack LA, and Temple WJ. (2009) A prospective evaluation of venous thromboembolism in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. <i>Canadian Journal of Surgery</i> 52:18-22	Case series n = 60  Follow-up: NR  includes cancers of appendix, colon/rectum, primary peritoneum, endocrine/small intestine or peritoneal mesothelioma	VTE: 10% (6/60)	Larger studies included in table 2
Rossi CR, Deraco M, De SM et al. (2004) Hyperthermic intraperitoneal intraoperative chemotherapy after cytoreductive surgery for the treatment of abdominal sarcomatosis: clinical outcome and prognostic factors in 60 consecutive patients. <i>Cancer</i> 100:1943-1950.	Case series n = 60  Follow-up: 28 months (median)  abdominal sarcomatosis	No postoperative deaths, morbidity: 33%  Overall median survival: 34 months	Larger studies included in table 2
Jacquet P, Stephens AD, Averbach AM et al. (1996) Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated with cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. <i>Cancer</i> 77:2622–9.	Case series n = 60  Follow-up: NR  (includes 16 with pseudomyxoma peritonei).	Postoperative mortality = 5%. Postoperative morbidity = 35%.	Larger studies included in table 2  [Included in Appendix A in original overview]  Patients also likely to be included in Stephens et al, 1999.

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Article title	Study design / number of patients/ follow-up / origin of cancer	Direction of conclusions	Reasons for non-inclusion in table 2
Roviello F, Marrelli D, Neri A et al. (2006) Treatment of peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion (IHCP): postoperative outcome and risk factors for morbidity. World Journal of Surgery 30:2033-2040.	Case series n = 59  Follow-up: mean:25 +/- 19 months, range: 1-68 months  24 ovarian, 19 colorectal, 12 gastric, 3 pseudomyxoma and 1 mesothelioma	Major morbidity: 27.9% Reoperation required: 8.2%  Complications include: acute renal failure: 2, arrhythmias: 2	Larger studies included in table 2
Glehen O, Mithieux F, Osinsky D et al. (2003) Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. Journal of Clinical Oncology 21:799-806.	Case series n = 56  Follow-up: NR	2-year survival: 79% with macroscopic resection and 44.7% without macroscopic resection.	Larger studies included in table 2
Fujimoto S, Takahashi M, Mutou T et al. (1996) Treatment failures after intraperitoneal hyperthermic perfusion combined with surgery for advanced gastric cancer. Regional Cancer Treatment 9:164-9.	Case series n = 54  Follow-up: NR	At follow-up, 43% (23/54) patients alive.	Larger studies included in table 2  [Included in Appendix A in original overview]  Patients also likely to be included in Fujimoto S, et al. 1997.
Glehen O, Cotte E, Schreiber V et al. (2004) Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. British Journal of Surgery 91:747-54.	Case series n = 53  Follow-up: 59.5 months (median)	Morbidity = 23% Mortality = 4% Overall median survival = 12.8 months.	Larger studies included in table 2  [Included in Appendix A in original overview]
Ceelen WP, Peeters M, Houtmeyers P et al. (2008) Safety and efficacy of hyperthermic intraperitoneal chemoperfusion with high-dose oxaliplatin in patients with peritoneal carcinomatosis. Annals of Surgical Oncology 15:535-541.	Case series n = 52  Follow-up: 14.5 months (mean) 33 colorectal, 9 ovarian, 4 pseudomyxoma, 4 mesothelioma and 2 gastric	Major morbidity: 24% 30-day mortality: 0% In colorectal patients, 1-year survival: 80%	Larger studies included in table 2

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<b>Article title</b>	<b>Study design / number of patients/ follow-up / origin of cancer</b>	<b>Direction of conclusions</b>	<b>Reasons for non-inclusion in table 2</b>
Yan TD and Morris DL. (2008) Cytoreductive surgery and perioperative intraperitoneal chemotherapy for isolated colorectal peritoneal carcinomatosis: experimental therapy or standard of care? Annals of Surgery 248:829-835.	Case series  n = 50  Follow-up: 14 months (range: 1-56 months)  colorectal	Overall median survival: 29 months 3-year survival: 39%	Larger studies included in table 2

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## Appendix B: Related NICE guidance for Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Guidance	Recommendations
Interventional procedures	<p><b>Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique). NICE interventional procedures guidance 56 (2004).</b></p> <p>1.1 Current evidence on the safety and efficacy of complete cytoreduction for pseudomyxoma peritonei does not appear adequate for this procedure to be used in the NHS outside centres funded by the National Specialist Commissioning Advisory Group (NSCAG).</p> <p>1.2 Clinicians wishing to undertake complete cytoreduction for pseudomyxoma peritonei should take the following action:</p> <ul style="list-style-type: none"> <li>• Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's <i>Information for the Public</i> is recommended.</li> <li>• Audit and review clinical outcomes of all patients having complete cytoreduction for pseudomyxoma peritonei.</li> </ul> <p>1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.</p> <p>1.4 These recommendations apply only to the use of this technique to treat pseudomyxoma peritonei. The Institute will consider complete cytoreduction for peritoneal carcinomatosis separately.</p>
Clinical guidelines	<p><b>Guidance on cancer services: Improving outcomes in colorectal cancer (manual update). NICE clinical guideline CSGCC (2004).</b></p> <p>Key Recommendations:</p> <ul style="list-style-type: none"> <li>• Action should be taken to improve recognition of potential symptoms of colorectal cancer in primary care and in the community. Efficient systems should be set up to ensure that patients who may have colorectal cancer are rapidly referred for endoscopy.</li> <li>• There is an urgent need for substantial expansion of lower gastrointestinal (GI) endoscopy services. Access to both flexible sigmoidoscopy and colonoscopy should be improved and the focus of diagnostic effort should move from barium enema to endoscopy. (Note - This will be crucial for screening services when they are introduced.)</li> </ul>

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	<ul style="list-style-type: none"><li>• Cancer Networks and Trusts should review the composition and function of colorectal cancer multi-disciplinary teams (MDTs) and make sure that each MDT has a co-ordinator. They should:<ul style="list-style-type: none"><li>• Establish systems within Trusts to ensure that <i>all</i> patients with suspected or newly diagnosed colorectal cancer are promptly referred to, and managed by, a colorectal cancer MDT.</li><li>• Review operational links with hepatobiliary (HPB) services and the relevant clinical teams to ensure that patients with potentially resectable liver metastases are referred to specialist MDTs for assessment.</li><li>• Identify specialist MDTs which will manage patients with anal cancer.</li></ul></li><li>• Emergency patients (particularly those with intestinal obstruction) should be managed by colorectal cancer MDTs. This may require the development of emergency teams and transfers of patients between neighbouring hospitals.</li><li>• Patients with rectal cancer should be managed by teams trained in all aspects of total mesorectal excision (TME), including pre and post-operative assessment, surgical technique, and the role of clinical oncology.</li><li>• All aspects of patient-centred care should be re-assessed in the light of recommendations in this manual update. In particular, Trusts should:<ul style="list-style-type: none"><li>• Improve the provision of appropriately trained staff and resources;</li><li>• Ensure that patients receive all the information they want at all times;</li><li>• Arrange ongoing support for patients and carers from a clinical nurse specialist who is encouraged to play an active part in MDT discussions.</li></ul></li></ul>
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## Appendix C: Literature search for Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	13/05/2009	Issue 2, 2009	2
Database of Abstracts of Reviews of Effects – DARE (CRD website)	13/05/2009	N/A	5
HTA database (CRD website)	13/05/2009	N/A	2
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	13/05/2009	Issue 2, 2009	12
MEDLINE (Ovid)	13/05/2009	1950 to May Week 1 2009	323
MEDLINE In-Process (Ovid)	13/05/2009	May 12, 2009	48
EMBASE (Ovid)	13/05/2009	1980 to 2009 Week 19	253
CINAHL (NLH Search 2.0 or EBSCOhost)	13/05/2009	N/A	51
BLIC (Dialog DataStar)	13/05/2009	N/A	8

Websites searched on 14/05/2009

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – surgical (ASERNIP-S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

### MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1	Peritoneal Neoplasms/
2	(periton* adj3 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinom\$ or tumour\$ or tumor\$ or malignan\$)).tw.
3	1 or 2

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4	Injections, Intraperitoneal/
5	(intraperiton* adj3 inject*).tw.
6	4 or 5
7	chemo*.tw.
8	6 and 7
9	(sugarbaker adj3 techniqu*).tw.
10	((intraperiton* or intra-periton*) adj3 chemo*).tw.
11	Combined Modality Therapy/
12	(combin* adj3 modalit* adj3 therap*).tw.
13	(multimod* adj3 treat*).tw.
14	or/8-13
15	cytoreduct*.tw.
16	debulk*.tw.
17	15 or 16
18	3 and 14 and 17
19	Animals/ not Humans/
20	18 not 19
21	limit 20 to ed=20040201-20090513

IP overview: cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis