

# NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### Interventional procedures overview of complete cytoreduction (Sugarbaker technique) for pseudomyxoma peritonei

#### ***Introduction***

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by one or more specialist advisors and review of the contents of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

#### ***Date prepared***

This overview was prepared by Bazian Ltd in October 2002

Updated by NICE March 2004

#### ***Procedure name***

- Complete cytoreduction combined with heated intraoperative intraperitoneal chemotherapy (Sugarbaker technique) in patients with pseudomyxoma peritonei.

#### ***Specialty society***

- Association of Upper Gastrointestinal Surgeons.

#### ***Description***

##### **Indications**

Pseudomyxoma peritonei is rare, occurring in about one person per million per year. It is a slowly progressive tumour arising from the appendix or bowel that spreads throughout the peritoneal cavity and produces a large amount of mucus. The appearance at surgery is often described as 'jelly belly'. The condition is considered borderline malignant. While most people with pseudomyxoma peritonei will eventually die of the condition, disease progression may be slow, some people surviving for several years after diagnosis. However, most people will develop symptoms caused by the bulk of the tumour.

##### **Summary of procedure**

This technique was developed by Paul Sugarbaker at the Washington Cancer Institute. It may improve symptom-free survival. It involves complete surgical tumour removal (also known as complete cytoreduction) combined with intraoperative heated chemotherapy during surgery, followed by postoperative intraperitoneal chemotherapy. The operation takes about 10 hours to complete and includes:

- removal of the right hemicolon, spleen, gall bladder, greater omentum and lesser omentum

- 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.

The traditional surgical approach is debulking, in which the surgeon attempts to remove as much tumour as possible, and usually removes the right hemicolon, and uterus and ovaries in women. Disease recurrence is very common. People often need several debulking operations.

People with pseudomyxoma peritonei may also be treated using a 'watch and wait' policy, involving surgery only when unacceptable symptoms or life-threatening complications such as intestinal obstruction arise.

## ***Literature review***

### **Appraisal criteria**

A search was made for articles describing the Sugarbaker technique, or operations describing complete cytoreduction and intraperitoneal chemotherapy if the name Sugarbaker was not cited.

Case series including fewer than 40 people were excluded. Many of the studies found included patients with peritoneal tumours other than pseudomyxoma peritonei.

### **List of studies found**

No controlled studies were found.

Five case-series authored by Paul Sugarbaker were found that met the inclusion criteria.<sup>1-5</sup>

Three case-series by other authors using techniques similar to the Sugarbaker technique were found that met the inclusion criteria.<sup>6-8</sup>

These eight case-series are summarised in Table 1. Relevant studies that have been excluded from the summary table are listed in Appendix A.

Since this overview was prepared, the NHS Health Technology Assessment Programme has published a study on the clinical effectiveness of the Sugarbaker technique for the treatment of pseudomyxoma peritonei.<sup>9</sup> This report is summarised in Table 2.

**Table 1 Summary of key efficacy and safety findings**

Study details	Key efficacy findings	Key safety findings	Comments
<p><b>Sugarbaker PH<sup>1</sup></b></p> <p>Case series</p> <p>Washington, USA</p> <p>Date 1989 to 1999</p> <p>n = 385 adults with pseudomyxoma peritonei, age not provided</p> <p>Mean follow up: 38 months</p>	<p>5 year survival:</p> <ul style="list-style-type: none"> <li>• with less malignant pathology (adenomucinosis): 86%</li> <li>• with more malignant pathology: (mucinous adenocarcinoma): 50%</li> </ul>	<p><b>Complications:</b></p> <ul style="list-style-type: none"> <li>• perioperative death (perioperative not defined) (2%)</li> <li>• pancreatitis (7%)</li> <li>• fistula formation (5%)</li> <li>• anastomotic leaks (2%)</li> </ul>	<p>Large case series.</p> <p>5-year survival not presented for all 385 patients; divided by pathology.</p> <p>Not clear how 5 year survival was calculated – mean follow up was 38 months.</p>
<p><b>Esquivel J<sup>2</sup></b></p> <p>Case series</p> <p>Washington, USA</p> <p>Date 1985 to 1997</p> <p>n = 321 adults with pseudomyxoma peritonei, age not provided</p> <p>Follow up period: not provided</p>	<p>5 year survival: 74% (in the 98 patients who underwent reoperation)</p> <p>Repeat cytoreductive surgery: 31%</p>	<p>Complications not described</p>	<p>Patients may overlap with those included in reference 1.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p><b>Sugarbaker PH<sup>3</sup></b></p> <p>Case series</p> <p>Washington, USA</p> <p>Date not stated (published 1996)</p> <p>n = 120 adults with pseudomyxoma peritonei, aged 27 to 76</p> <p>Mean follow up: 2 years</p>	<p>Recurrence at mean follow up 2 years: 38%</p> <p>Survival: not provided</p>	<p>Postoperative death (postoperative not defined): 3%</p> <p>Intestinal fistula that failed to close after 1 month: 6%</p>	<p>Patients may overlap with those included in reference 1.</p>
<p><b>Zoetmulder F<sup>4</sup></b></p> <p>Case series</p> <p>Washington, USA</p> <p>Date 1985 to 1998</p> <p>n = 118 adults with pseudomyxoma peritonei, age 29 to 61</p> <p>Median follow up: 2 years</p>	<p>Recurrence: 36%</p>	<p><b>Complications</b> (data on 32 patients analysed in detail):</p> <ul style="list-style-type: none"> <li>• Pleural spread related to initial surgery: 6/32</li> <li>• Recurrence in laparotomy scar: 15/29 patients evaluated</li> <li>• Recurrence in suture lines 15/25 patients evaluated</li> </ul>	<p>Patients may overlap with those included in reference 1.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p><b>Sugarbaker PH<sup>5</sup></b></p> <p>Case series</p> <p>Washington, USA</p> <p>Date 1991 to 1992</p> <p>n = 69 adults, aged 28 to 77</p> <ul style="list-style-type: none"> <li>• pseudomyxoma peritonei (38)</li> <li>• peritoneal carcinoma (31)</li> </ul> <p><b>follow-up: up to 10 years</b></p>	<p>3 year overall survival: 70%</p> <p>3 year survival in people with pseudomyxoma peritonei: 90%</p> <p>3 year overall recurrence: 45%</p>	<p>Complications (number of people):</p> <ul style="list-style-type: none"> <li>• small bowel fistula (8)</li> <li>• anastomotic leakage (2)</li> <li>• urine leakage (1)</li> <li>• duodenal leakage (1)</li> <li>• gastrooesophageal reflux (2)</li> <li>• subphrenic abscess (1)</li> <li>• postoperative bleeding (3)</li> <li>• pancreatitis (1)</li> <li>• central venous catheter sepsis (2) leading to one death</li> <li>• bile leakage (1)</li> <li>• peritonitis (1)</li> <li>• left hepatic artery ligated (1)</li> </ul>	<p>Included people with peritoneal carcinoma as well as pseudomyxoma peritonei.</p> <p>No intraoperative heated chemotherapy given.</p> <p>Patients may overlap with those included in reference 1..</p>
<p><b>Parvaiz A<sup>5</sup></b></p> <p>Case series</p> <p>Basingstoke, UK</p> <p>Date 1994 to 2000</p> <p>n = 62 people, age not provided</p> <ul style="list-style-type: none"> <li>• pseudomyxoma peritonei (54)</li> <li>• adenocarcinoma (4)</li> <li>• mesothelioma (3)</li> <li>• leiomyoma (1)</li> </ul> <p><b>follow up: not specified</b></p>	<p>No survival results given</p>	<p>3 postoperative deaths out of 43 people who had complete tumour removal and intraperitoneal chemotherapy</p>	<p>Reported as abstract only.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p><b>Zoetmulder FAN'</b></p> <p>Case series</p> <p>Amsterdam, The Netherlands</p> <p>Date not stated (published 1999)</p> <p>n = 53 adults</p> <ul style="list-style-type: none"> <li>• pseudomyxoma peritonei (29)</li> <li>• peritoneal carcinomatosis of colorectal origin (24)</li> </ul> <p>Median follow up:</p> <ul style="list-style-type: none"> <li>• pseudomyxoma peritonei: 12 months</li> <li>• peritoneal carcinomatosis: 18 months</li> </ul>	<p><b>Pseudomyxoma peritonei patients:</b></p> <p>Survival at 12 months: 72%</p> <p>Disease free survival at 12 months: 62%</p> <p><b>Peritoneal carcinomatosis patients:</b></p> <p>Survival at 18 months: 86%</p> <p>Disease free survival at 18 months: 52%</p>	<p>Complications (no further detail available):</p> <p>pseudomyxoma peritonei patients: 28%</p>	<p>Included people with peritoneal carcinoma as well as pseudomyxoma peritonei.</p> <p>Limited data available: information obtained from English abstract of paper published in Dutch.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p><b>Witkamp AJ<sup>8</sup></b></p> <p>Case series</p> <p>Amsterdam, The Netherlands</p> <p>Date 1996 to 2000</p> <p>n = 46 adults with pseudomyxoma peritonei, age 34 to 76</p> <p>Median follow up: 12 months</p>	<p>Survival at 12 months: 95%</p> <p>Local recurrence: 19%</p>	<p><b>Complications</b> (number of people):</p> <ul style="list-style-type: none"> <li>• stomach or bowel perforation (10)</li> <li>• enteral fistula (6)</li> <li>• pancreatitis (1)</li> <li>• pulmonary embolism (3)</li> <li>• peripheral pressure neuropathy (5)</li> <li>• pneumonia (3)</li> <li>• abscess (4)</li> <li>• reoperation for postoperative complications (11)</li> <li>• multiple, persistent enteral fistulas requiring prolonged parenteral feeding at home (1)</li> <li>• postoperative death (4)</li> <li>• neutropenia (22)</li> <li>• thrombocytopenia (4)</li> <li>• prolonged gastric paresis ('almost all patients')</li> </ul> <p>Mean blood loss 13 litres</p>	<p>Small case series.</p>

Table 2 Summary of key efficacy and safety findings of a systematic review published after the consultation period

Studies details	Key efficacy findings	Key safety findings	Comments
<p><b>Bryant J<sup>9</sup></b></p> <p>Systematic review</p> <p>Literature search date: September 2002</p> <p>5 case-series included:                      Ronnett et al, 2001 (n = 109)<sup>10</sup>                      Smith et al, 1992 (n = 17)<sup>11</sup>                      Sugarbaker et al, 1993 (n = 38)<sup>5</sup>                      Sugarbaker, 2001 (n = 385)<sup>12</sup>                      Witkamp et al, 2001 (n = 46)<sup>8</sup></p> <p>Reported mean follow-up ranged from 27.2 months to 95.7 months.</p> <p>Inclusion criteria: patients with pseudomyxoma peritonei characterised by histologically benign tumours with indolent course originating in the appendix.</p>	<p><b>Survival:</b></p> <ul style="list-style-type: none"> <li>• 3-year survival: 81%, 88%, 89.5%</li> <li>• 5-year survival: 75%, 75%, 86%</li> <li>• 10-year survival: 60%, 68%</li> </ul> <p><b>No evidence of disease:</b></p> <ul style="list-style-type: none"> <li>• 41% (7/17) (mean follow-up 62 months)</li> <li>• 52% (34/65) (mean follow-up 96 months)</li> <li>• 70% (32/46) (median follow-up 12 months)</li> </ul> <p><b>Alive with disease:</b></p> <ul style="list-style-type: none"> <li>• 9% (6/65) (mean follow-up 96 months)</li> <li>• 17% (8/46) (median follow-up 12 months)</li> <li>• 35% (6/17) ( mean follow-up 62 months)</li> </ul> <p><b>Dead of disease:</b></p> <ul style="list-style-type: none"> <li>• 2% (1/46) (median follow-up 12 months)</li> <li>• 24% (4/17) (mean follow-up 62 months)</li> <li>• 31% (20/65) (mean follow-up of 96 months)</li> </ul>	<p><b>Complications</b></p> <ul style="list-style-type: none"> <li>• Starch peritonitis: 6% (1/17)</li> <li>• Stomach or bowel perforation: 22% (10/46)</li> <li>• Enteral fistula: 13% (6/46)</li> <li>• Pancreatitis: 2% (1/46)</li> <li>• Pulmonary embolism: 6% (3/46)</li> <li>• Peripheral pressure neuropathy: 11% (5/46)</li> <li>• Pneumonia: 6% (3/46)</li> <li>• Intra-abdominal or wound abscess: 9% (4/46)</li> </ul> <p>In one study of 46 patients, adjuvant chemotherapy was discontinued in 18% of patients who received it, owing to intolerable toxicity.</p>	<p>This report was published after the consultation period for this procedure</p> <p>No controlled studies met the inclusion criteria for the systematic review</p> <p>Four studies were not based on a representative sample and one was unclear</p> <p>Four studies were judged to be unclear on adequacy of follow-up</p> <p>Most of the series were small, and some spanned many years</p> <p>Only two studies reported morbidity data</p> <p>Different histological subgroups may have been included</p> <p>Details of cytoreductive surgery and chemotherapy differed within and between studies</p>



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

- All the publications that were found on the technique were case series. These provide useful information on the complications of treatment but the effectiveness of the procedure remains uncertain compared with conventional surgical techniques or 'watch and wait'.
- Five of the studies reported on patients operated on at the same hospital during overlapping time periods.<sup>2-6</sup> It is not clear how many of the patients are described in more than one report.
- Three of the studies<sup>6-8</sup> included patients with other peritoneal malignancy as well as people with pseudomyxoma peritonei. These types of peritoneal malignancy are likely to have a worse prognosis, so the results in these patients are not generalisable to people with pseudomyxoma peritonei. In one of the studies,<sup>6</sup> no intraoperative chemotherapy was given. It therefore evaluates a different procedure to the Sugarbaker technique.

### ***Bazian comments***

- The Sugarbaker technique is very radical surgery that may cause major morbidity. Its effects compared with more conservative approaches have not been established.

### ***Specialist advisors' opinions***

Specialist advice was sought from consultants who have been nominated or ratified by their Royal College or Specialist Society.

- There is international controversy about the effectiveness of the procedure, given the slow natural history of pseudomyxoma peritonei.
- Preoperative accurate diagnosis of pseudomyxoma peritonei is difficult.
- The Sugarbaker technique is very expensive because of the training required, the length and complexity of surgery, and the need for intensive care and total parenteral nutrition. Because of these costs, and the rarity of the disease the Specialist Advisors considered a national treatment centre would be appropriate.

## References

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11. Smith JW, Kemeny N, Caldwell C, Banner P, et al. Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer Center experience. *Cancer* 1992; 70: 396 – 401.
12. Sugarbaker PH. Cytoreductive surgery and perioperative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. *Eur J Surg Oncol* 2001; 27: 239 – 243.

Appendix A: references for relevant studies excluded from summary table

Reference	Number of patients
Sugarbaker PH. Cytoreduction including total gastrectomy for pseudomyxoma peritonei. <i>British Journal of Surgery</i> 2002; 89(7): 208-212.	45
Cavaliere F, Di Filippo F, Consolo S, Cairella G, et al. Integrated treatment of peritoneal carcinomatosis. <i>Chirurgia</i> 1999; 12(2):87-91.	31
Glehen O, Peyrat P, Beaujard A, Caillot JL, et al. Abdominal cancer with peritoneal carcinomatosis treated by peritonectomy procedure and intraperitoneal chemohyperthermia. <i>Eksperimentalnaia Onkologija</i> 2000; 22(1-2):59-63.	22
Gilly FN, Beaujard A, Glehen O, Grandclement E, et al. Peritonectomy combined with intraperitoneal chemohyperthermia in abdominal cancer with peritoneal carcinomatosis: phase I-II study. <i>Anticancer Research</i> 1999; 19(3B):2317-21.	18
Piso P, Bektas H, Werner U, Schlitt HJ, et al. Improved prognosis following peritonectomy procedures and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from appendiceal carcinoma. <i>European Journal of Surgical Oncology</i> 2001; 27(3):286-90.	17
Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. Natural history and presentation of a curative approach to treatment. <i>Diseases of the Colon &amp; Rectum</i> 1987; 30(10):772-9.	14
Butterworth SA, Panton ONM, Klaassen DJ, Shah AM, et al. Morbidity and mortality associated with intraperitoneal chemotherapy for Pseudomyxoma peritonei. <i>American Journal of Surgery</i> 2002; 183(5):529-32.	11
Hosch WP, Rudi J, Stremmel W. Therapy of pseudomyxoma peritonei of appendiceal origin - Surgical resection and intraperitoneal chemotherapy. <i>Zeitschrift fur Gastroenterologie</i> 1999; 37(7):615-22.	10
Sanz CM, Sugarbaker PH. Adenocarcinoid of appendiceal origin causing peritoneal carcinomatosis. <i>Regional Cancer Treatment</i> 1994; 7(3-4):211-6.	7
Glehen O, Mithieux F, Osinsky D, Beaujard AC, et al. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. <i>Journal of Clinical Oncology</i> 2003; 21 (5): 799-806.	7
Marchettini P, Sugarbaker PH. Mucinous adenocarcinoma of the small bowel with peritoneal seeding. <i>European Journal of Surgical Oncology</i> 2002; 28(1):19-23.	6
Nasr MF, Kemp GM, Given Jr FT. Pseudomyxoma peritonei: Treatment with intraperitoneal 5-fluorouracil. <i>European Journal of Gynaecological Oncology</i> 1993; 14(3):213-7.	4
Chen MY, Chiles C, Loggie BW, Choplin RH, et al. Thoracic complications in patients undergoing intraperitoneal heated chemotherapy with mitomycin following cytoreductive surgery. <i>Journal of Surgical Oncology - Supplement</i> 1997; 66(1):19-23.	3