

# Systematic review of the Sugarbaker procedure for pseudomyxoma peritonei

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**Background:** Pseudomyxoma peritonei, a rare progressive disease process within the peritoneum, is characterized by an abundance of mucinous fluid; if left untreated, the condition is fatal. The aim of this article is to assess the clinical effectiveness and costs of the Sugarbaker procedure for pseudomyxoma peritonei.

**Methods:** A systematic review of the literature up to April 2004 was undertaken, with modelling of costs.

**Results:** Five retrospective case-series reports met the inclusion criteria. Survival after operation was approximately 95 per cent at 2 years and 60–68 per cent at 10 years, with 41–52 per cent of patients having no evidence of disease at the end of follow-up. A Monte Carlo simulation model estimated the marginal cost for one patient over a maximum of 5 years to be about £9700 (standard deviation £1300).

**Conclusion:** Evidence of the effectiveness of the Sugarbaker procedure for pseudomyxoma peritonei is limited in quantity and quality, but suggests there may be some benefit for patients. The marginal cost of the operation is about £9700, provided that trained and experienced staff are available to perform the procedure.

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## Introduction

Pseudomyxoma peritonei, a progressive disease within the peritoneum, is characterized by the production of copious amounts of mucinous fluid that gradually fills the peritoneal cavity, resulting in the characteristic 'jelly belly'<sup>1</sup>. The condition is thought to originate from an appendiceal adenoma within the appendiceal lumen that continues to grow until it occludes<sup>2</sup>. Eventually the appendix ruptures and mucus containing epithelial cells from the adenoma slowly leaks out by means of a process known as disseminated peritoneal adenomucinosis. Although the primary tumour may change little in size, epithelial cells continue to proliferate, seeding the peritoneal cavity with mucus-producing cells and resulting in distinctive peritoneal tumours. The resulting large quantities of soft, translucent, mucinous material produced over several years within the peritoneum collect at predictable abdominal and pelvic sites; this is known as the redistribution phenomenon<sup>3,4</sup>. Almost inevitably, pseudomyxoma peritonei leads to progressive obliteration

of the peritoneal cavity and intestinal obstruction, which is fatal without treatment<sup>3</sup>.

The specific definition, pathology, site of origin and prognosis of pseudomyxoma peritonei are uncertain. Originally the term was used to describe mucinous ascites associated with ruptured appendiceal mucoceles, but over time has become broader and is often applied to any condition that results in extensive mucus accumulation within the abdomen regardless of the organ of origin and malignancy<sup>2,3,5</sup>. Recently it has been recognized that such a broad-ranging definition is not helpful in understanding the natural history of pseudomyxoma peritonei or in developing treatments. It has consequently been suggested that the term should be applied only to tumours emanating from the appendix, and with a pathology of disseminated peritoneal adenomucinosis in which tumour cells appear low grade, are relatively scant, and do not invade organs or lymph nodes<sup>6</sup>.

Pseudomyxoma peritonei is a rare condition, with approximately 50 new cases in the UK each year. It

affects men and women equally, with an increasing incidence with age (South West Cancer Intelligence Service, unpublished data 2004). Median survival is approximately 6 years, with 50–70 per cent of patients surviving for 5 years and 10–32 per cent for 10 years<sup>2</sup>. Prognosis varies with the nature of the tumour and recurrences are common<sup>2</sup>. Patients most commonly present with symptoms suggesting acute appendicitis or increasing abdominal girth<sup>5,7</sup>.

Standard treatment consists of debulking surgery, repeated as necessary, to reduce tumour mass and mucin production<sup>1</sup>. This treatment is not curative but aims to resect all gross disease to limit the build-up of mucus and its pressure effects. Recurrence of the disease requires repeated and progressively more difficult surgery owing to adhesions and fibrosis. A more aggressive strategy involving more radical surgery, and intraperitoneal and systemic chemotherapy, has been adopted by some clinicians, aiming for cure. The Sugarbaker procedure<sup>1</sup> was developed on this basis. It consists of six peritonectomy procedures, performed as necessary to rid the abdomen of disease, including greater omentectomy–splenectomy, stripping of the left and right hemidiaphragm, cholecystectomy and lesser omentectomy, antrectomy and pelvic peritonectomy with resection of the rectosigmoid colon. Intraperitoneal chemotherapy with mitomycin C, which may be heated to 40–44°C, is a component of the treatment. This is instilled into the peritoneal cavity and distributed over all surfaces by continuous manipulation of the viscera by the surgeon's hand over a period of 90 min. Further chemotherapy is administered in the first few days after surgery.

Treatment for pseudomyxoma peritonei remains controversial, with a range of proposed alternatives and continually evolving surgical procedures. Uncertainty persists regarding the clinical effectiveness of the different approaches and the way in which any service should be organized. The National Health Service (NHS) Health Technology Assessment Programme commissioned, on behalf of the National Specialist Commissioning Advisory Group (NSCAG), a systematic review and economic evaluation to examine the clinical effectiveness of the Sugarbaker procedure for treating pseudomyxoma peritonei and the costs of the procedure in the UK. This paper summarizes and updates issues identified by the review<sup>8</sup>.

### Patients and methods

Twelve electronic databases, including Medline, PubMed, Embase, Cochrane Systematic Reviews database, Cochrane Controlled Trials Register and Database of Abstracts of Reviews of Effectiveness, were searched for the

period up to April 2004. Medline and Cochrane Library keywords and medical subject heading (MeSH) terms used were 'pseudomyxoma or peritoneal adenomucinosis ((pseudomyxoma) or (periton\* near adenomucinosis))'. The strategy was adapted as appropriate for other databases. Additional studies were identified by searching bibliographies of related publications and by contact with experts. Further details are available elsewhere<sup>8</sup>.

English-language experimental and observational studies were sought that included traditional resection surgery to debulk all gross disease, cytoreductive surgery combined with chemotherapy, or cytoreductive surgery combined with heated adjuvant intraperitoneal chemotherapy. The studies should have included people diagnosed as having pseudomyxoma peritonei characterized by histologically benign tumours with an indolent course originating in the appendix. They must have used patient-based primary outcomes of survival, recurrence or quality of life, and complications as a secondary outcome, with a minimum of 2 years' follow-up. Published economic evaluations and costing studies were also sought. The quality of studies was assessed using criteria recommended by the NHS Centre for Reviews and Dissemination (University of York)<sup>9</sup>. Decisions about inclusion criteria, quality criteria and data extraction were made by one reviewer and checked by a second, with disagreements resolved through discussion.

Reported data were combined by narrative synthesis with full tabulation of included studies. Meta-analysis was not appropriate because of lack of a comparator, and pronounced heterogeneity in patient characteristics and comparative interventions. Owing to lack of statistically verifiable data, the economic study was limited to modelling the likely costs based on information from the present study, comments from experts in the USA, and UK sources. The model used a Monte Carlo simulation technique to handle uncertainty, by which a probability distribution for each variable in the model was derived using cost estimates and assumptions about resource use and survival time<sup>10</sup>. A cohort of 1000 treated patients, using a different value for each data-input randomly selected from that variable's probability distribution, was generated. All simulated patients were then compiled into a set of forecasts to give an expected cost per patient. Estimates to populate the model were made using unit prices from a local NHS hospital for staff, intensive care and ward costs. Capital and overhead costs were excluded. Thus the marginal cost of providing treatment for pseudomyxoma peritonei using the Sugarbaker procedure rather than standard treatment was derived; details have been reported elsewhere<sup>8</sup>.

## Results

### Quantity and quality of evidence

Five retrospective case-series reports<sup>6,11-14</sup>, published between 1992 and 2003, met the inclusion criteria (Table 1); no study examining standard debulking surgery or comparing the Sugarbaker procedure with standard treatment met the inclusion criteria. When judged using standard criteria for assessing methodological quality, the included studies were found to be of poor quality (Table 2). Quality assessment showed that four were not based on a representative sample and one was unclear; four did not use explicit *a priori* inclusion criteria. Two studies did not report whether patients were at a similar point in disease progression, with the remaining studies being unclear, and all five studies were judged unclear on adequacy of follow-up. All five studies were also unclear when reporting whether outcomes were assessed objectively or whether blinding was used. The one study with subseries analysis did not provide sufficient description of the series and the distribution of prognostic factors.

Most of the series were small, with only two including more than 50 patients, and some spanned many years. Although all patients had pseudomyxoma peritonei of

appendiceal origin, lack of histological detail may mean that different histological subgroups were included. Details of cytoreductive surgery and chemotherapy differed between the studies, and not all patients within a series received the same treatment.

### Assessment of clinical effectiveness

#### Survival

The included studies reported survival at varying time intervals after different treatment regimens (Table 3). The 2-year survival rate was reported as 95 per cent for patients treated with cytoreduction and heated intraperitoneal chemotherapy with mitomycin C<sup>12</sup>. Three-year survival rates were reported as 89 per cent in a series of patients receiving cytoreduction and heated intraperitoneal chemotherapy<sup>12</sup>, 88 per cent in those receiving cytoreduction and heated intraperitoneal chemotherapy<sup>11</sup>, and 90 per cent in those receiving cytoreduction plus intraperitoneal chemotherapy with or without further intraperitoneal chemotherapy or intravenous chemotherapy<sup>14</sup>.

A 5-year survival rate of 70 per cent was reported for patients treated with cytoreduction and heated intraperitoneal chemotherapy with mitomycin C<sup>12</sup>. In

**Table 1** Case series of treatment for pseudomyxoma peritonei

Reference	Year	Intervention	Subjects	Follow-up
Ronnett <i>et al.</i> <sup>6</sup>	2001	CR + IPEC (MMC and 5-FU) early after surgery + three cycles of adjuvant systemic MMC and IPEC with 5-FU	PMP (disseminated peritoneal adenomucinosi) ( <i>n</i> = 65)	Mean 95.7 months
Smith <i>et al.</i> <sup>13</sup>	1992	CR + IPEC ( <i>n</i> = 4) and intravenous chemotherapy ( <i>n</i> = 6)	PMP ( <i>n</i> = 17)	Mean 62 (range 4–120) months
Sugarbaker <i>et al.</i> <sup>14</sup>	1993	CR + IPEC (MMC) + 5-FU	PMP ( <i>n</i> = 38)	Not known
Sugarbaker <sup>11</sup>	2001	CR + HIPEC (MMC)	PMP (adenomucinosi) ( <i>n</i> = 224)	Mean 37.6 months
van Ruth <i>et al.</i> <sup>12</sup>	2003	CR + HIPEC (MMC)	PMP (disseminated peritoneal adenomucinosi) ( <i>n</i> = 38)	Median 33 (range 3–75) months

CR, cytoreduction; IPEC, intraperitoneal chemotherapy; MMC, mitomycin C; 5-FU, 5-fluorouracil; PMP, pseudomyxoma peritonei; HIPEC, hyperthermic intraperitoneal chemotherapy.

**Table 2** Methodological quality of case series using National Health Service Centre for Reviews and Dissemination case series quality assessment criteria

Reference	Representative sample	Inclusion criteria	Disease progression	Follow-up	Objective outcomes	Subseries analysis
Ronnett <i>et al.</i> <sup>6</sup>	No	No	?	?	?	NA
Smith <i>et al.</i> <sup>13</sup>	No	No	?	?	?	NA
Sugarbaker <i>et al.</i> <sup>14</sup>	No	No	?	?	?	NA
Sugarbaker <sup>11</sup>	No	No	No	?	?	No
van Ruth <i>et al.</i> <sup>12</sup>	?	Yes	No	?	?	NA

?, Unclear; NA, not applicable.

**Table 3** Effectiveness of treatment for pseudomyxoma peritonei

Reference	Survival rate (%)				Disease status (%)	
	2 years	3 years	5 years	10 years	No evidence of disease	Alive with disease
Ronnett <i>et al.</i> <sup>6</sup>			75	68	52	9
Smith <i>et al.</i> <sup>13</sup>			75	60	41	35
Sugarbaker <i>et al.</i> <sup>14</sup>		90			NK	NK
Sugarbaker <sup>11</sup>		88	86 (complete cytoreduction)		NK	NK
van Ruth <i>et al.</i> <sup>12</sup>	95	89	70		44 (at 3 years' follow-up)	

NK, not known.

two studies the 5-year survival rate was reported as 75 per cent; in one study patients underwent cytoreduction and early intraperitoneal chemotherapy (mitomycin C and 5-fluorouracil (5-FU), followed by three cycles of adjuvant systemic mitomycin C and intraperitoneal chemotherapy with 5-FU)<sup>6</sup>, and in the other study all patients had cytoreductive surgery with some receiving intraperitoneal chemotherapy and others having intravenous chemotherapy<sup>13</sup>. A third study<sup>11</sup> showed a 5-year survival rate of 86 per cent after complete cytoreduction and maximal heated intraperitoneal chemotherapy.

Reported 10-year survival rates were 68 per cent after cytoreduction and early intraperitoneal chemotherapy (mitomycin C and 5-FU) followed by three cycles of adjuvant systemic mitomycin C and intraperitoneal 5-FU<sup>6</sup>, and 60 per cent after cytoreductive surgery and either intraperitoneal chemotherapy or intravenous chemotherapy<sup>13</sup>.

#### Mortality and recurrence

Death from disease occurred in 24 per cent<sup>13</sup> and 31 per cent<sup>6</sup> of patients in the studies that reported this outcome at variable follow-up (Table 4). At the end of follow-up, 41 per cent<sup>13</sup> and 52 per cent<sup>6</sup> of patients were disease-free, and 9 per cent<sup>6</sup> and 35 per cent<sup>13</sup> were alive with disease (Table 3). One study<sup>12</sup> reported a 3-year disease-free rate of 44 per cent.

#### Complications and morbidity

The reporting of morbidity resulting from treatment was not consistent across studies, but the most commonly mentioned complications were anastomotic leaks, fistula formation, wound infection, small bowel obstruction and perforation, and pancreatitis.

**Table 4** Mortality and morbidity from treatment for pseudomyxoma peritonei

Reference	Died from disease (%)	Died from other causes (%)	Morbidity (%)
Ronnett <i>et al.</i> <sup>6</sup>	31	8	
Smith <i>et al.</i> <sup>13</sup>	24		6
Sugarbaker <i>et al.</i> <sup>14</sup>	NK		
Sugarbaker <sup>11</sup>	NK		
van Ruth <i>et al.</i> <sup>12</sup>	NK		

NK, not known.

#### Costs

No economic evaluations were identified. One 1996 study from the USA reported the total cost of treatment for pseudomyxoma peritonei using the Sugarbaker procedure as \$166 922 (range \$72 795–185 464)<sup>1</sup>. This study had limited generalizability as the evidence was of low quality, not based on data from a randomized controlled trial or comparative observational study, and the setting was specific to the USA where charge data were used to simulate costs.

In the absence of economic evaluations, utility studies and randomized controlled trial data of the Sugarbaker procedure compared with standard treatment, a simple economic model using Monte Carlo simulation was developed to give the likely marginal cost of treatment in the UK<sup>8</sup>. This model did not include the costs of setting up the specific service or training staff. The results of this simulation model showed that the marginal cost, without capital and overhead costs, for one patient over a maximum of 5 years would be about £9700 (standard deviation £1300). The most likely factor influencing the variation in costs was the operating time. There is no evidence available to compare these results to those of an alternative treatment.

## Discussion

This review, guided by an advisory panel of experts, considered systematically the evidence of the effectiveness of the Sugarbaker procedure for pseudomyxoma peritonei. The literature relating to pseudomyxoma peritonei was found to be limited, with no randomized controlled trials, other comparative studies or studies of standard debulking. Pseudomyxoma peritonei is a rare condition and, not surprisingly, its study consists of only a few small case series. The published studies included in this review are retrospective case series of generally poor quality when judged using the criteria recommended by the NHS Centre for Reviews and Dissemination, such as how representative study samples are, inclusion criteria, disease state, follow-up and use of objective outcomes.

A major difficulty concerns the definition of pseudomyxoma peritonei. This term has been applied broadly and includes a heterogeneous group of pathological lesions. Different pathological definitions are associated with a single morphology; there is little consensus on whether pseudomyxoma peritonei should be classified as malignant or not, and on the point of separation between pseudomyxoma peritonei and carcinomatosis peritonei due to high-grade mucinous carcinoma. This review has tried to include groups of patients who were histologically and prognostically similar by applying the narrow definition of pseudomyxoma peritonei as disseminated peritoneal adenomucinosis and excluding peritoneal carcinomatosis and hybrid variants. A number of studies identified during the review included patients from different pathological subgroups, such as pseudomyxoma/adenocarcinoma variant and mucinous carcinoma, in addition to those with disseminated peritoneal adenomucinosis. Unfortunately, as results were not presented separately for each subgroup, these studies had to be excluded from review. Even so, it is still possible that any variation in outcome between different case series may be explained by differences in disease severity. Also, it is not clear from the literature whether each study represented a separate cohort of patients.

In addition to the general methodological problems described above, there are particular issues associated with assessing a surgical intervention, such as the ethics of blinding patients by using sham surgery, and surgeon- and technique-related variables<sup>15</sup>. Surgical treatments are less standardized than drug treatments, and are dependent on the skill of the surgeon. The results achieved by international experts may not be replicated in routine clinical practice. Within the studies included in the review, patients were at different points in the disease process and underwent different procedures to obtain maximal cytoreduction, and different courses of chemotherapy in

terms of route and timing. Some had already received treatment for pseudomyxoma peritonei, often at a different institution, making it difficult to assess the impact of current treatment. Some studies spanned decades, during which time surgical procedures were evolving. Repeat operation for recurrence of pseudomyxoma peritonei is more demanding, with a consequent impact on results.

There are also problems associated with length of follow-up. In most studies follow-up was likely to have been inadequate for all important events to occur for all patients. Often details of methodology were not clear. In particular, rationale was often omitted for defining the start and end-points of follow-up for the different cohorts of patients. Differences in defining follow-up impact on the assessment of outcomes, increasing uncertainty about the comparability of different studies.

Despite the limitations of the data, the results suggest that there may be some benefit for patients with pseudomyxoma peritonei who undergo treatment with the Sugarbaker procedure. Results of the Monte Carlo simulation model showed that the marginal cost for one patient over a maximum of 5 years would be about £9700 with certain assumptions. These results contrast radically with the US study, the sum being about one-tenth of the American value. However, the studies have different settings, and the present review used a health technology assessment-based cost concept, which is more compliant to an opportunity cost perspective than accountancy charges. The economic results give an example of the likely UK marginal costs of the Sugarbaker procedure and do not include costs incurred in setting up a specific service, such as training and developing appropriate teams and specialist equipment. In addition to training, teams need to be involved in performing the procedure on a regular basis to maintain their skill level. Other factors to be considered are the heavy demands placed on the intensive care and high dependency units by patients with pseudomyxoma peritonei undergoing the Sugarbaker procedure. Finally, the exposure of health workers to low-dose intraoperative chemotherapy must be considered.

Decision-making about radical treatment for a rare condition is difficult, especially when evidence on clinical and cost effectiveness is problematic. In the UK the Sugarbaker procedure for pseudomyxoma peritonei has been considered by the Interventional Procedures Advisory Committee of the National Institute for Clinical Excellence. Guidance issued in April 2004<sup>16</sup> states that 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 NSCAG. Clinicians wishing to undertake the Sugarbaker technique for pseudomyxoma peritonei must ensure that their patients understand the uncertainty about the safety and efficacy of the procedure, and provide them with clear written information. These clinicians should also audit and review clinical outcomes of all patients having complete cytoreduction for pseudomyxoma peritonei. After a review of services in the UK by NSCAG, a second designated national centre opened in April 2002 to help meet the growing national demand and offer improved patient access<sup>17</sup>. Future high-quality prospective research, ideally an evaluation of the Sugarbaker procedure *versus* less radical surgery, including costs, would be valuable.

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