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Recurrence and outcome after complete tumour removal and hyperthermic intraperitoneal chemotherapy in 512 patients with pseudomyxoma peritonei from perforated appendiceal mucinous tumours

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Abstract

Background: Pseudomyxoma peritonei (PMP) usually originates from perforated mucinous appendiceal tumours and may present unexpectedly at surgery, or be suspected at cross sectional imaging. The optimal treatment involves macroscopic tumour removal by cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The 10-year Kaplan–Meier predicted disease-free survival is 61%. Some patients with recurrence are amenable to further CRS and HIPEC.
Aim: To evaluate the outcomes of re-do surgery in a large single centre series of reoperation for recurrence of peritoneal surface malignancy.
Method: Retrospective analysis of prospective database of 752 patients undergoing CRS for perforated appendiceal tumours analysed. Routine follow up involved annual CT scans and serum tumour marker measurement. The survival and recurrence in the 512/752 (68.1%) who had complete cytoreduction between March 1994 and January 2012 was calculated by Kaplan–Meier univariate analysis.
Results: Overall 137/512 (26.4%) developed recurrence and of those 35/137 (25.5%) underwent repeat surgery. Complete tumour removal was again achieved in 20/35 (57.1%). There were no postoperative deaths and no significant difference in early postoperative complications and length of stay compared to primary CRS surgery. The 5-year survival in the 375 without recurrence, the 35 who had re-do surgery and the 102 who had recurrence with no surgery was 90.9%, 79.0% and 64.5% respectively.
Conclusion: Approximately one in four patients develops recurrence after complete CRS and HIPEC for PMP of appendiceal origin. Selected patients can undergo salvage surgery with good outcomes.

Keywords: Pseudomyxoma peritonei; Peritoneal neoplasms; Mucinous; Recurrence; Peritoneal malignancy; Surgery

Introduction

Pseudomyxoma peritonei (PMP) is a rare neoplastic condition, commonly presenting with mucinous ascites and diffuse peritoneal deposits. The exact incidence is unknown but has been estimated to be around 1 to 3 per million per year.[1] PMP most commonly originates from a perforated mucinous appendiceal tumour, though it can arise from other mucinous abdominal tumours, most commonly an ovarian or colorectal primary.[2] Due to the indolent nature of PMP in many cases, patients may present with vague symptoms of abdominal distension and pain, often leading to a late diagnosis. PMP is invariably fatal if not optimally treated. Not uncommonly PMP may be diagnosed from unexpected findings at surgery, or discovered incidentally at cross sectional imaging.

Repeated tumour debulking surgery was the traditional mainstay of treatment but in recent years there have been significant advances in definitive surgery for PMP with the combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) now considered the optimal treatment.[3]

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Sugarbaker was the first to describe and popularize the strategy of aggressive macroscopic tumour removal CRS combined with HIPEC in 2001.[2] The techniques have been widely adopted in specialist units for PMP and have also been utilized extensively for other peritoneal malignancies, particularly colorectal peritoneal metastases.[4,5]

A recent multicentre retrospective analysis of 2289 patients from 16 specialist units outlined the success of the combined strategy of complete macroscopic tumour removal combined with HIPEC, reporting 10 and 15 year survivals of 63% and 59% respectively with an acceptable treatment-related mortality of 2%.[7] These results are in contrast to reports on a strategy of repeated debulking surgery with a 10 year survival of 31% and similar operative mortality.[8]

Despite these outcomes after CRS and HIPEC, a significant proportion of patients will recur. Due to small absolute numbers in most units, the presentation and outcome of PMP patients with recurrence has not been widely reported. Zoetmulder and colleagues reported that 42 of 118 patients presented with recurrence after a median follow up period of 1.9 years.[9] Smeenk et al. reported 17 patients undergoing repeat cytoreduction for recurrence and proposed a benefit in repeat CRS and HIPEC with a three year survival of 100% compared with 53.3% if CRS and HIPEC were not performed.[10] They also noted better outcomes in patients who had a longer disease free period prior to recurrence. Yan et al. found that 28% of patients developed progressive disease during follow up. The majority of these patients underwent repeat surgery and perhaps not surprisingly had improved survival if complete cytoreduction was again achieved.[11]

The decision to carry out repeated major abdominal surgery in PMP patients who recur after CRS and HIPEC is complex as they are likely to have significant adhesions and altered anatomy. The success rates and long term outcomes of repeated surgery are currently not clearly defined. Most previous studies have included small numbers of patients undergoing re-do surgery.[10,12] This study aims to evaluate the immediate and long term outcomes in a relatively large subset of patients who recurred following complete CRS and HIPEC for PMP of appendiceal origin.

Patients and methods

This was a retrospective cohort analysis of a prospectively maintained database of patients undergoing CRS for perforated appendiceal tumours at a single specialist centre. Data was analysed over an 18 year period from 1994 to 2012. Inclusion criteria were patients who had complete cytoreduction at primary surgery for pseudomyxoma peritonei of appendiceal origin. CRS involves extensive peritonectomies, including right and left diaphragmatic peritonectomy with greater and lesser omentectomy and resection of any directly involved part of the bowel or other non-essential organs.[6] Following completion of CRS, hyperthermic Mitomycin C chemotherapy is instilled into the peritoneal cavity for one hour prior to any bowel anastomosis. A complete cytoreduction was either complete macroscopic tumour removal (CC 0) or residual tumour nodules less than 2.5 mm in size (CC 1) as outlined previously whereby any remaining tumour is treatable by HIPEC.[13]

All patients are followed up and details recorded. Our routine follow up involves CT imaging and CEA, CA-125 and CA-19.9 serum tumour marker measurement at one year after surgery and annually thereafter for 10 years.

Patients with recurrence were considered for repeat surgery if the disease was thought to be resectable on review of the imaging by a specialist multidisciplinary team. In many cases apparent isolated recurrence was monitored for a period of 3–12 months to determine if disseminated recurrence manifested over time as initial experiences had shown that widespread diffuse disease was rarely amenable to complete removal due to diffuse small bowel involvement with a high complication rate, particularly small bowel fistulation.

The data were analysed using Statistical Package for the Social Sciences (version 20; IBM SPSS Inc, Chicago, IL, USA). Continuous data were expressed as median and range. Analyses of categorical data were performed using Mann–Whitney U test or Fisher's exact test where appropriate. Time-Events values were given in median and 95% confidence interval (95% CI); when mean was not reached in any group the means (and 95% CI) were given for all 3 groups. Survival was calculated from time of first complete cytoreduction to death. Cumulative survival rates were calculated by the Kaplan–Meier product limit method and the differences in survival between groups were tested for statistical significance using the Mantel–Cox log-rank test. A p value of less than 0.05 was deemed statistically significant.

Results

Between March 1994 and January 2012 a total of 752 patients underwent surgery for PMP of appendiceal origin. Of these 512/752 (68.1%) had complete cytoreduction and were included in the study. The remaining 240 patients had either maximal debulking surgery or laparotomy and biopsy only and were excluded. The median age was 56 (range: 24–82) There was a female: male ratio of 2:1.

Overall 137/512 (26.4%) of patients who had complete CRS developed recurrence during the follow up period of 39 months (range 12–180). Median time to recurrence was 26.3 months (95% CI: 22.8–29.7). During the study period 35/137 (25.5%) of patients with recurrence underwent repeat surgery. Complete tumour removal was again achieved in 20 of the 35 patients (57.1%). The division of patients into groups for comparison is illustrated in Fig. 1. The 5-year survival in the 375 without recurrence, the 35 who had re-do surgery and the 102 who had recurrence with no surgery was 90.9%, 79.0% and 64.5% respectively

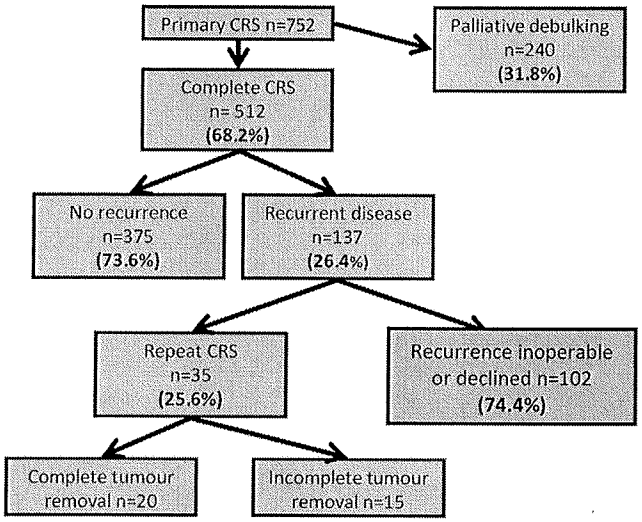

Figure 1. Flowchart showing division of patients into groups for comparison.

(Fig. 2) The mean overall survivals were 171.3 months (95% CI: 164–178), 129.5 months (95% CI: 105–153) and 100.6 months (84.2–119) respectively ($p = 0.001$).

There was no statistical difference in complication rates between the group undergoing repeat CRS and HIPEC compared to primary CRS and HIPEC. Comparative complications rates can be found in Table 1. *P* values were calculated using Fisher Exact Probability Test. Chest complications were defined as pneumonia or pleural effusion. Wound complications were defined as wound infection or wound dehiscence. The median Intensive Care Unit (ICU) stay was 2 days in both groups. There was no statistical difference in length of hospital stay (excluding ICU stay), with a median of 16 days after primary surgery compared to 14 days for re-do surgery. The median operative time was 10.5 h (range 4.0–15) for primary surgery and 8.0 h (range 3.5–16) for re-do surgery. *P* values were calculated using Mann–Whitney *U* Test.

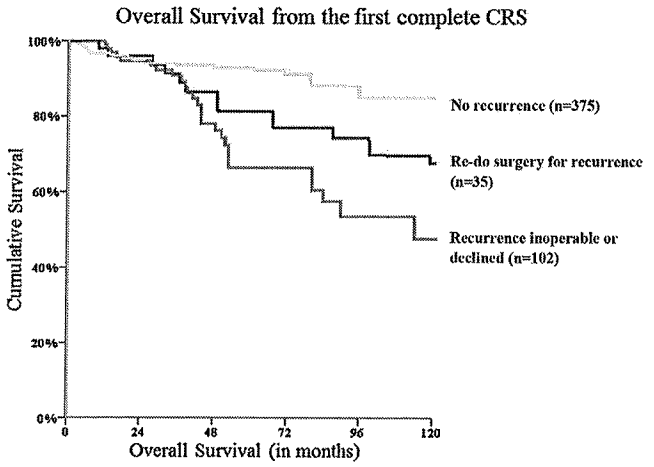

Figure 2. Kaplan–Meier curve showing survival in the three groups of patients.

Table 1
Complications in patients undergoing primary and re-do CRS.

Events	Re-do surgery for recurrence $N = 35$	Primary surgery $N = 512$	*P* value
Chest complications	4 (11.4%)	87 (17.0%)	0.448
Wound complications	5 (14.2%)	34 (6.6%)	0.093
Coagulopathy	2 (5.7%)	13 (2.5%)	0.248
Deep vein thrombosis	4 (11.4%)	57 (11.1%)	1.000
Pulmonary embolism	1 (2.9%)	9 (1.8%)	0.486
Intra-abdominal collection	1 (2.9%)	7 (1.4%)	0.412
Prolonged ileus	3 (8.6%)	26 (5.1%)	0.439

Discussion

This study reports the incidence of recurrence in a large cohort of patients undergoing CRS and HIPEC for PMP of appendiceal origin. The outcome in the proportion that recurred and underwent repeat surgery is reported and compared with those that did not recur and those that recurred and did not undergo, or declined re-intervention. Overall approximately one in four patients who had complete CRS and HIPEC for PMP of appendiceal origin recurred. The data reported here are comparable to previous publications with smaller numbers.[9]

A proportion of patients with recurrence may be suitable for salvage surgery aiming for further complete tumour removal, resulting in improved outcomes compared to those who are treated non-operatively. However there is substantial selection bias in these groups such that exact comparison is not possible and ideally a randomized controlled trial is required to determine the absolute benefit of re-do surgery. This is unlikely to be acceptable to patients and the small numbers in any unit are likely to make such a study impractical.

There are significant risks and technical difficulties associated with re-operative surgery in patients who have had CRS and HIPEC but nevertheless a re-do procedure in selected patients is achievable and likely to be beneficial. Selection of suitable patients is complex and best achieved in a specialist multidisciplinary setting. Suspected isolated recurrence may need to be monitored for several months prior to making a decision to re-operate as some patients progress to diffuse recurrence which would not be amenable to complete removal, often due to extensive diffuse involvement of the small bowel. The "trial by time" is also deemed useful as all current imaging modalities, including CT which is considered optimal, underestimate low volume disease. This concept is based on empirical observations during the course of this study. The decision to re-operate is based not only on the prediction of the technical possibility of a second complete cytoreduction but also each patient's personal wishes and fitness for further major surgery.

There were no postoperative deaths and no significant differences in early postoperative complications or length

Table 2
Operative time, length of stay and use of blood products and Total Parentaral Nutrition (TPN) in patients undergoing primary and re-do CRS.

Parameter (median and range)	Re-do surgery for recurrence. $N = 35$	Primary surgery $N = 512$	P value
Operative time	8.0 h (3.5–16)	10.5 h (4–14)	0.059
Blood transfusion	4 units (0–29)	2 units (0–169)	0.062
Other blood product transfusion	6 units (0–34)	5 units (0–58)	0.060
Duration of TPN	9.5 days (2–94)	9 days (3–50)	0.423
ICU stay	2 days (0–50)	2 days (0–94)	0.592
Hospital stay (excluding ICU)	14 days (3–46)	16 days (1–126)	0.267

of stay in patients undergoing re-do surgery compared with those who had primary CRS (Table 2).

In conclusion patients undergoing a second CRS procedure have low post-operative morbidity and mortality rates and when carefully selected the majority can have further complete macroscopic tumour removal. In this cohort of 35 who had re-operative surgery, one patient had three re-do procedures and 4 patients had 2 re-do procedures.

Research is ongoing to identify patients at higher risk of recurrence in order to both determine the most effective follow up regimen and develop improved primary treatment strategies such as systemic chemotherapy or post-operative intraperitoneal chemotherapy which might reduce this risk. Unsurprisingly high grade pathological grading of the resected specimen disease and a primary tumour of colorectal rather than appendiceal origin have been shown to be associated with a higher risk of recurrence.[14] Additionally a number of studies have shown that raised tumour markers (particularly CA19-9) at diagnosis suggest a poorer prognosis, with a higher risk of recurrence.[15–18]

A limitation of this study remains the small numbers. Continued data collection and analysis over a period of years is necessary to draw stronger conclusions as to the role of re-do surgery in the management of this challenging condition. The current report provides some information on the incidence of recurrence in a large series of patients with PMP of appendiceal origin and outlines areas in need of further evaluation in the complex area of detection and management of patients unfortunate enough to recur despite best efforts at the primary procedure.

Conflict of interest statement

None of the authors wish to declare any conflict of interest.

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