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Original Paper

Patterns of Failure Following Treatment of Pseudomyxoma Peritonei of Appendiceal Origin

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Pseudomyxoma peritonei is a rare disease caused by a perforated adenoma of the appendix. It results in extensive accumulation of mucinous tumour at specific locations within the abdomen and pelvis. The study was undertaken to examine patterns of recurrence in patients with grade I disease treated by cytoreductive surgery and early postoperative intraperitoneal chemotherapy. After a median follow-up of 1.9 years (range 0.5–7.4 years) 42 out of 118 patients had recurred. In 32 patients, detailed information regarding the anatomical location of recurrent tumour from CT-scan and second-look laparotomy were available and these form the basis of this study. The volume of recurrent tumour was recorded at eight abdominal sites, the laparotomy scar and at suture lines. Patient, tumour and treatment factors were analysed for a possible relationship with the pattern of recurrence. With recurrence, true metastatic disease was observed in 3 patients and a distinctly higher grade of intraperitoneal tumour in another patient. Pleural spread of pseudomyxoma was found in 6 patients, always related to entering the pleural cavity during cytoreduction ($P = 0.000031$). Two abdominal sites consistently had an increase in tumour deposits at re-operation as compared to the initial cytoreduction. Small bowel had large deposits at re-operation in 17% versus 3% at initial cytoreduction and retroperitoneal surfaces 10% versus 0%. Recurrences were most frequent in the left subhepatic/lesser omentum area (28%), while the right subdiaphragmatic area (3%) was least involved. Pseudomyxoma peritonei recurrence in the laparotomy scar was found in 15/29 patients (52%), significantly more frequent if tumour had been present at former laparotomy scars during cytoreduction ($P = 0.042$). In 15/25 (60%) of patients, recurrences were found at suture lines. Differences in the completeness of cytoreduction, inadequate distribution of intraperitoneal chemotherapy to upper abdominal and small bowel surfaces, and entrapment of tumour within suture lines were thought to be causal factors consistent with this pattern of recurrence. Consequences for future treatment strategies are discussed.

Key words: pseudomyxoma peritonei, peritoneal carcinomatosis, intraperitoneal chemotherapy, peritonectomy, cytoreductive surgery, 5-fluorouracil, mitomycin-C
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INTRODUCTION

PSEUDOMYXOMA PERITONEI is a rare clinical entity, characterised by massive production of mucus in the abdominal cavity from a perforated adenoma of the appendix [1]. The primary tumour in the appendix produces a mucocele which eventually bursts, spreading mucous-producing adenomatous epithelial cells throughout the abdomen and pelvis. Distribution of peritoneal adenomucinosis is by no means random, but appears to be controlled by the flow of peritoneal fluid and by the effects of gravity [2, 3]. As fluid moves through the peritoneal cavity, the mucus-producing epithelial cells tend to settle by gravity within dependent sites such as the *cul de sac*, the paracolic gutters and right subhepatic space. Also, cells move along with the peritoneal fluid towards the greater omentum and the undersurface of the diaphragm, where lymphatic inlets absorb peritoneal fluid. As a consequence of these mechanisms, tumour deposits are preferentially found

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on the greater omentum, subdiaphragmatic surfaces, small pelvis and paracolic gutters, while the visceral peritoneum of the small bowel remains completely free of disease. Wide distribution of tumour throughout the abdomen and pelvis may be explained by the lack of adhesive properties on the surface of these mucinous tumour cells, which prevents their adherence and growth close to the primary tumour as is usually observed in high grade cancers [3]. The motility of intestinal surfaces may dislodge mucinous tumour cells.

This lack of adherence is overcome at wound sites where the fibrin matrix may provide the basis for adhesions [4–6]. This may explain the other characteristic feature of pseudomyxoma distribution, its tendency to grow at wound sites, including both natural wounds, such as a ruptured ovarian follicle, and surgical wounds, such as intestinal adhesions or the abdominal incision.

The natural history of this disease is that of slow progression to death due to bowel dysfunction and cachexia [7–9]. Repeated debulking operations can delay the fatal outcome of the disease, sometimes for many years, but eventually patients die of uncontrollable intra-abdominal tumour growth, or of complications of surgery in the end phase of disease. A recent review by Gough and colleagues reported only 5% of patients surviving longer than 5 years after treatment by surgery alone [9].

Sugarbaker and colleagues have, over a number of years, studied the impact of aggressive cytoreductive surgery combined with intra-operative chemotherapy on this disease [1, 10–12]. This approach is based on the assumption that mucinous adenocarcinoma cells are only relatively resistant to chemotherapy, and will respond if the concentrations of 5-fluorouracil and mitomycin-C are sufficiently high. If tumour nodules on the peritoneum are surgically reduced to the size of millimeters, drugs delivered in the peritoneal cavity may reach these cells by diffusion in high concentrations, while plasma concentrations will remain below toxic levels [12].

In a recent paper, the outcome of 130 cases of mucinous appendiceal tumours with intraperitoneal dissemination, treated by cytoreductive surgery and chemotherapy, was reported [13]. Completeness of cytoreduction and grade of the malignancy were found to be the main determinants of outcome. In patients with grade 1 mucinous tumour and complete cytoreduction, the 3 year survival after intraperitoneal chemotherapy was over 80%. However, recurrence remains a frequent event, even in this group of patients with good prognosis. To reduce the frequency of recurrence it is important to know in detail where, and if possible understand why, the treatment failed. In this paper, we present an analysis of 32 patients with pseudomyxoma peritonei who recurred after treatment with a complete cytoreduction followed by early postoperative chemotherapy with mitomycin-C and 5-fluorouracil.

PATIENTS AND METHODS

Data were derived from the database of patients with pseudomyxoma peritonei treated by a single surgeon (PHS) in the period from 1985 to January 1995. For this analysis, patients were only considered if they had undergone a complete cytoreduction for grade 1 pseudomyxoma peritonei and had received at least one cycle of early postoperative intraperitoneal chemotherapy [11–13]. In the study period, 118 patients fell into this category, with a median follow-up of 1.9 years (range 0.5–7.4 years). Of these patients, 42 developed tumour recurrences. Detailed information on the pattern of recurrence was available in 32 patients, by laparotomy and CT-scan, in cases of intra-abdominal recurrence (29 cases), or by CT-scan or biopsy in cases of extra-abdominal recurrences (3 cases). Data on these 32 patients are the basis for this study. Clinical features on these patients are given in Table 1.

Tumour grading

Only grade 1 mucinous tumours in both the appendix and distant intra-abdominal sites were included in this series. Grade 1 tumours are cystadenomas with abundant mucin with free floating epithelial cells, either individually or in small clusters. These cells may be columnar or goblet in nature, but do not show signet ring configuration. Follicles of mucin are lined with a predominantly single layer of cells. There may be some nuclear pallisading, but the cells are bland looking and there are no mitotic figures and minimal atypia. The histology is consistent with the fact that pseudomyxoma peritonei is a disease whose primary tumour is a perforated appendiceal adenoma [14].

Tumour distribution at primary cytoreduction

Detailed information was available on the distribution of tumour throughout the peritoneal cavity in all patients. The presence and amount of tumour was recorded in nine anatomical sites: greater omentum and spleen area; under surface left diaphragm, space between right diaphragm and liver; subhepatic and lesser omentum area; ileocaecal area including right paracolic gutter; small pelvis including rectosigmoid, left paracolic gutter, uterus and adnexa; small bowel and mesentery; retroperitoneum. Also, the presence of tumour at former laparotomy sites were recorded. Tumour masses larger than 5 cm were recorded as large, masses between 0.5 cm and 5 cm were recorded as moderate, and tumours smaller than 0.5 cm were recorded as small.

Table 1. Clinical features of 32 patients with recurrences after complete resection and intraperitoneal chemotherapy for pseudomyxoma peritonei of appendiceal origin

Number of patients	32
Mean age (years)	43.4
Range	29–61
Gender	
Male	17
Female	15
Primary site	
Appendix	28
Uncertain	4
Median interval first pseudomyxoma operation to cytoreduction	2.7 years (range 0.1–16.4)
Number of previous operations for pseudomyxoma	
1	25
2	4
3	2
>6	1
Mean interval between cytoreduction and recurrence	1.8 years (range 0.5–5.5)

Cytoreduction

Cytoreductive surgery has evolved considerably during the time under which patients have been treated. The extent of the peritonectomy surgery was directly related to the distribution of tumour found at laparotomy. The peritonectomy techniques used have been described in detail elsewhere [15]. The peritoneal areas described above correspond to the main peritonectomy procedures: resection of greater omentum and spleen; peritonectomy of the undersurface of the left diaphragm; peritonectomy of the undersurface of the right diaphragm; resection of tumour from the left subhepatic and lesser omentum area, if needed including distal gastrectomy; ileocaecal resection, including the right paracolic gutter; peritonectomy of the small pelvis usually including rectosigmoid, left paracolic gutter, uterus and adnexa. Tumour nodules on the small bowel were scraped off the bowel surface. Involved laparotomy sites were excised leaving the umbilicus intact. The number and type of peritonectomies in each patient were recorded, as well as suture lines made during the reconstruction. The entry criteria of this study required all patients to have undergone a complete cytoreduction. Complete was defined as tumour remnants smaller than 0.25 cm in greatest dimension.

Early postoperative intraperitoneal lavage and chemotherapy

All patients were treated to limit postoperative adhesion formation in order to improve exposure of peritoneal surfaces to the drugs. After the cytoreduction was completed, a Tenckhoff catheter was positioned for infusion and three closed suction drains for drainage. Immediately after closure of the abdominal incision, the abdomen was lavaged with an hourly infusion and drainage of 1 litre of dextrose 1.5% peritoneal dialysis fluid, until draining fluid was clear. On postoperative day 1, mitomycin-C, at a dose of 10 mg/m^2 with a maximum of 20 mg dissolved in 1 litre of 1.5% dextrose, was infused as a peritoneal dialysis solution into the peritoneal cavity. After 23 h, the drains were opened and all remaining fluid was removed by gravity drainage. From day 2 until 5 the same procedure was followed using 5-fluorouracil at a dose of 15 mg/kg with a maximum of 1500 mg. All patients included in this series completed this first cycle.

Adjuvant intraperitoneal 5-fluorouracil and mitomycin-C therapy

All 18 patients treated prior to October 1992 received, after complete recovery, additional cycles of adjuvant chemotherapy. These cycles were given on a monthly basis with intraperitoneal 5-fluorouracil at a dose of 20 mg/kg and a maximum dose of 1600 mg over 5 days. Mitomycin-C was given intravenously as a 2-h infusion at a dose of 10 mg/m^2 with a maximum dose of 20 mg on day 3 of the cycle. 2 patients received two cycles of adjuvant chemotherapy and the remainder received three cycles.

Interval between primary cytoreduction and recurrence evaluation

In patients whose recurrences were evaluated by surgery, the time interval between cytoreductive surgery and second laparotomy was recorded. In patients who were evaluated by CT-scan or biopsy, the time interval between cytoreduction and the diagnosis of recurrence was recorded.

Evaluation of recurrence

Full information on the distribution of recurrences over the abdominal cavity was available in 29 patients who underwent a second laparotomy. The presence and size of tumour at the eight intra-abdominal sites and at the laparotomy site were recorded. In 25 patients, the presence and size of recurrences at suture lines could be evaluated. In 2 patients, no suture lines were made and in 3 patients, the data were incomplete. In 3 cases with extra-abdominal recurrences, only CT-scan and biopsy data were available.

Statistical analysis

The following factors were analysed for a possible impact on the pattern of recurrence: patient factors including age at first presentation and gender; tumour factors including interval between first presentation of pseudomyxoma and cytoreduction, size and distribution at first cytoreduction over eight abdominal areas and the previous laparotomy site; surgical factors including number of peritonectomies, number and type of suture lines, entrance into the pleural cavity; intraperitoneal chemotherapy factors including whether patients received adjuvant chemotherapy or not.

Factors analysed for their impact on the following endpoints observed at the time of recurrence evaluation were the presence or absence of distant metastases, the presence or absence of pleural metastases, the presence or absence of large or moderate size tumor recurrences at eight areas in the abdomen, the presence or absence of large or moderate size implants at the laparotomy site and the presence or absence of large or moderate size suture line recurrences.

Statistical significance was assessed using Fisher's exact and Chi square tests. Differences were considered significant at a level of $P < 0.05$.

RESULTS

Tumour distribution at primary cytoreduction

Massive amounts of tumour were present in all but 2 patients at the time of cytoreductive surgery. Figure 1 is a composite diagram that shows the distribution and size of tumour nodules in the eight abdominal areas and the laparotomy scar. Large tumour deposits (>5 cm) were present in 54% of the recorded intra-abdominal areas. Large tumour deposits were significantly less common on the small bowel (3%) and retroperitoneum (0%) compared to the other areas (72%) (Chi squared: $P < 0.0001$). Major peritonectomy procedures were carried out in all but 2 patients. In 11 patients, all 6 peritonectomy procedures were performed; in 7 patients 5 procedures were used; in 6 patients 4 procedures were used; in 3 patients, 3 procedures were used; and in 5 patients less than 3 procedures were used. As part of the cytoreductive operations, 82 suture lines were made, an average of 2.6 per patient (range 0–5). Common suture lines were: gastroenterostomy (11), pyloroplasty (12), small bowel anastomoses (4), ileocolic anastomoses (21), colocolic anastomoses (2), colorectal anastomoses (23) and vaginal cuff closure (9). During peritonectomy of the subdiaphragmatic spaces, part of the diaphragm was resected or the pleura space was entered in 8 patients. An attempt was made to close these defects in the diaphragm in a watertight manner in all patients. At the end of the cytoreductive operation, no tumour at all was visible in 5 patients. In all other patients nodules smaller than 0.25 cm were left, usually at innumerable sites. The most common site of these small residual mucinous tumour nodules was the small bowel (26 patients).

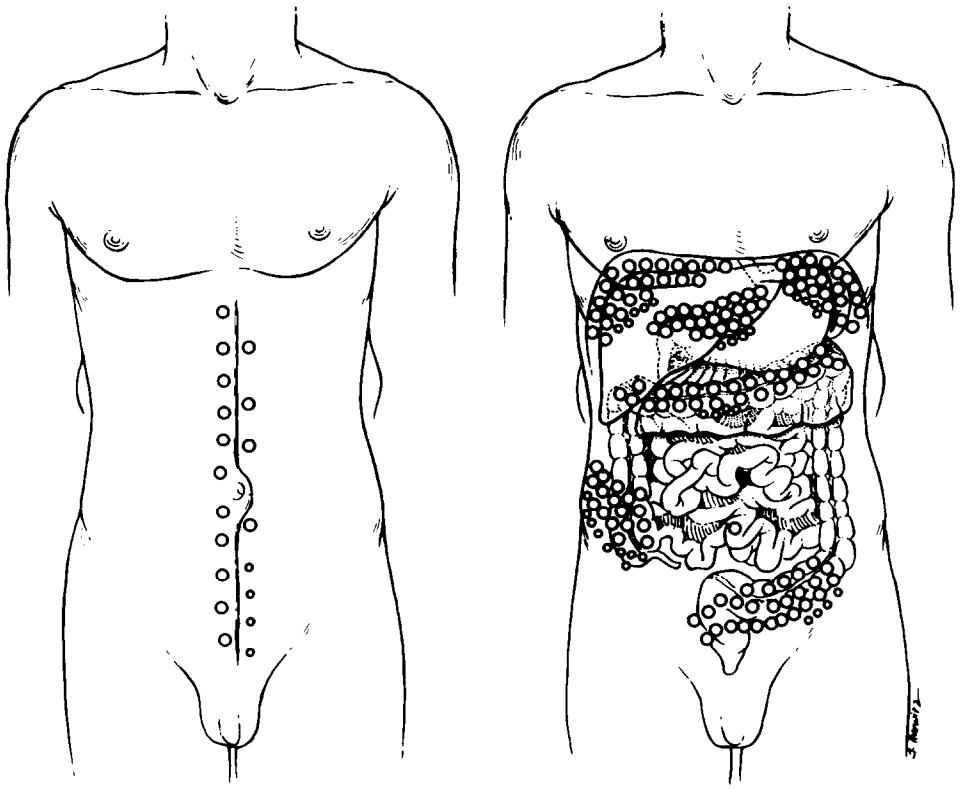

Figure 1. Laparotomy scar and tumour distribution at eight abdominal areas at cytoreductive surgery in 32 patients. Each large ○ represents 1 patient with a tumour mass larger than 5 cm in the area depicted. Each small ○ represents 1 patient with a tumour mass of 0.5–5 cm in the area depicted.

Interval

The mean interval between cytoreduction and intraperitoneal chemotherapy and recurrence was 1.8 years (range 0.5–5.5 years).

Tumour grading of recurrences in the abdomen and pelvis

Histology was obtained in 30 of the 32 recurrences. In 26 cases, the tumour continued as grade 1. In 2 patients, only mucus was found without any epithelial cells. In 2 patients, a higher tumour grade was found. In 1 patient, abdominal recurrence showed signet cell differentiation. Another patient had lymph node metastases in the small bowel mesentery and inguinal nodes. In both of these patients, at repeat laparotomy, the mucinous tumour grade was changed from grade 1 to 3.

Metastases

True metastatic disease was found in 3 patients. In 2 patients, intrapulmonary metastases were found and 1 patient (mentioned in the preceding paragraph) developed inguinal and small bowel mesentery lymph node metastases. No histology was obtained from the lung metastases. None of the tested variables predicted the development of metastases.

Pleural spread

6 patients developed pleural spread of pseudomyxoma. In all but 1 patient, intra-abdominal tumour deposits were also present. None of the patient or tumour factors predicted the development of pleural metastases. However, pleural metastases occurred significantly more often when the diaphragm was opened during primary cytoreduction. Of 8 patients in whom the pleural space was entered, 6 developed pleural nodules (75%), always on the same side as the diaphragm penetration. No pleural dissemination occurred if the diaphragm had remained intact (Fisher's exact test: $P = 0.000031$).

Intra-abdominal recurrences

In 29 patients who underwent a second laparotomy, a detailed assessment of abdominal tumour recurrences could be made. Figure 2 is a composite diagram that shows the sites and size of recurrences over the eight abdominal areas and the laparotomy scar. Large tumour deposits (>5 cm) were found in 15% of the abdominal areas recorded (54% of the abdominal areas had large tumour invasions at cytoreduction). Figure 3 presents a comparison of the data in Figures 1 and 2 for large tumour deposits at nine different anatomical sites at primary cytoreduction and at re-operation. There was a clear reduction at the greater omentum/spleen, left and right subdiaphragmatic, subhepatic/lesser omentum, ileocaecal and pelvic areas (15% versus 72%, Chi squared: $P < 0.0001$). The reduction was most prominent in the right subdiaphragmatic area (3% versus 75%), and least prominent in the subhepatic/lesser omentum area (28% versus 78%). However, there was an increase in the number of patients with large deposits on the small bowel and retroperitoneum (14% versus 2%, Fisher's exact test: $P = 0.013$). In none of the patients did tumour or treatment variables predict for differences in the distribution or size of recurrences over the eight abdominal areas. Data gathered for moderate sized tumour nodules showed a similar distribution (data not shown).

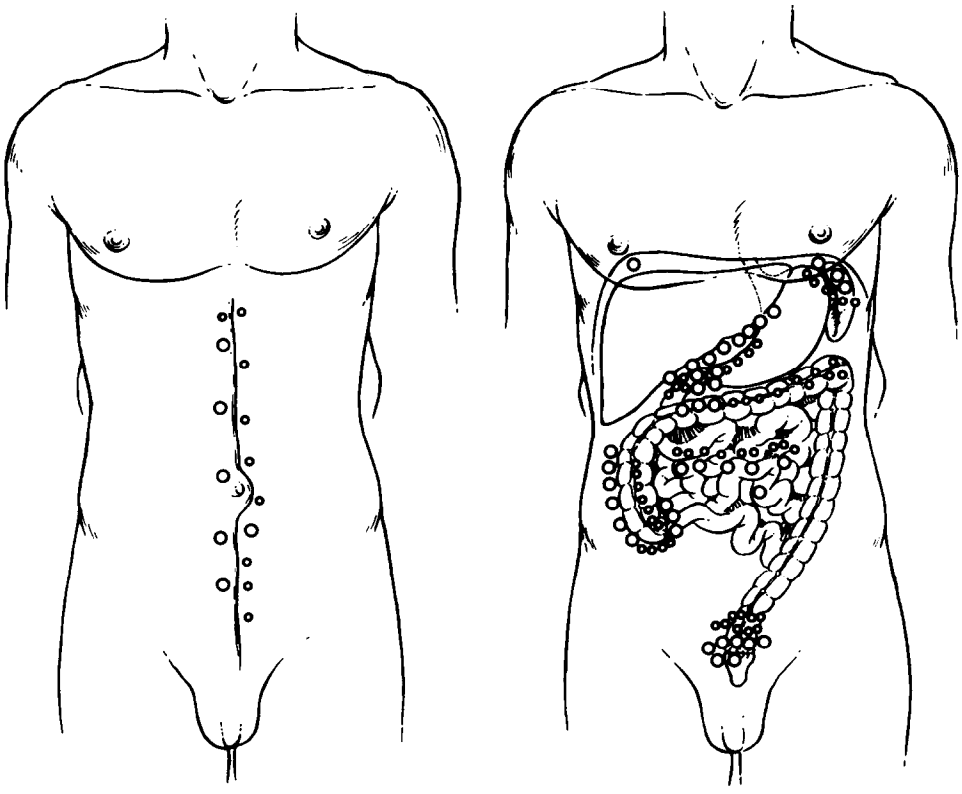

Figure 2. Tumour distribution at the laparotomy scar and at eight abdominal sites at second laparotomy in 29 patients. Each large ○ represents 1 patient with a tumour mass larger than 5 cm in the area depicted. Each small ○ represents 1 patient with a tumour mass of 0.5–5 cm in the area depicted.

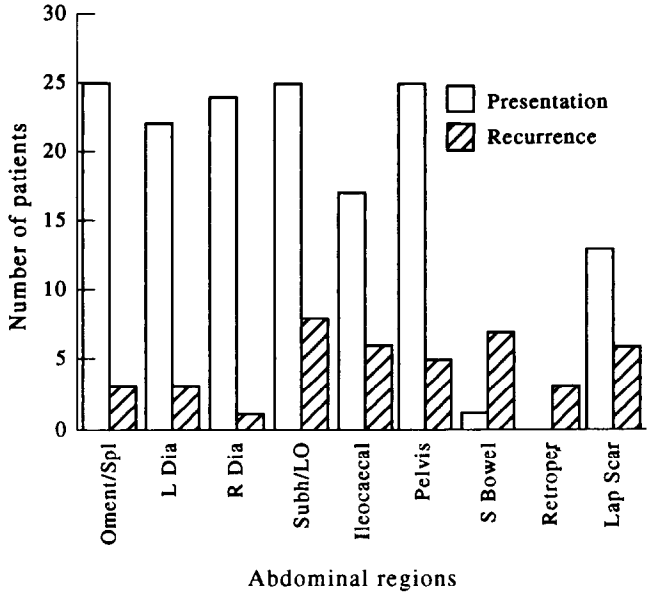

Figure 3. Histogram showing the number of patients with large tumour deposits (>5 cm) at eight abdominal areas and the laparotomy scar at presentation during cytoreductive surgery (32 patients) and at laparotomy for recurrence (29 patients). Abdominal regions: Oment/Spl, omentum/spleen; L Dia, left subdiaphragm; R Dia, right subdiaphragm; Subh/LO, subhepatic/lesser omentum; S Bowel, small bowel; Retroper, retroperitoneal; Lap Scar, laparotomy scar.

Implants at laparotomy scar

Large or moderate size recurrences at the laparotomy site were found in 15 patients. None of the patients or treatment factors predicted significantly for the development of tumour implants at the laparotomy site. Of the tumour factors, only tumour growth at the scar of previous laparotomies at the first cytoreduction operation showed some predictive value. Of 16 patients who originally presented with major tumour growth at the laparotomy scar, 11 again developed tumour growth at this site as part of the recurrence pattern, while only 4 out of 13 patients who did not present with tumour at the original laparotomy site did so (Fisher's exact test: $P = 0.042$).

Tumour recurrences at suture lines

Fifty-nine suture lines made during cytoreduction in 25 patients could be evaluated for recurrence. Suture line recurrences were observed in 15 patients (60%). Recurrences were observed in 18 (31%) of the suture lines made in these patients during cytoreduction. Recurrences were found in 41% of suture lines in the upper abdomen (gastroenterostomy: 4 out of 8; pyloroplasty: 2 out of 7; small bowel: 1 out of 2; ileocolic: 7 out of 17) compared to 17% of suture lines in the lower abdomen (colorectal: 1 out of 15; vaginal cuff: 3 out of 8). In addition, there were six recurrences in suture lines that had been made during prior surgical interventions and that showed no obvious signs of involvement at the time of cytoreduction. They were distributed as follows: 1 small bowel anastomosis; 1 ileocolic anastomosis, and 1 at an appendectomy site; 1 colocolic anastomosis; 1 vaginal cuff closure and 1 colorectal anastomosis. Possible factors that might influence the occur-

rence of suture line metastases were separately tested for suture lines in the upper abdomen and suture lines in the lower abdomen. No patient or tumour factors were found that related to the development of suture line recurrences. None of the surgical factors showed an impact, except of course the presence of suture lines in itself. Patients who had received only 1 cycle of intraperitoneal chemotherapy tended to have more suture line recurrences than patients who received more than 1 cycle. Suture line recurrences in the upper abdomen occurred in 5/7 patients (71%) receiving only 1 cycle and in 6/14 patients (43%) receiving more than 1 cycle. Suture line recurrences in the lower abdomen occurred in 2/6 (33%) patients after only 1 cycle and in 1/12 patients (8%), who received more than 1 cycle. These differences were statistically non-significant.

DISCUSSION

Until recently, treatment of pseudomyxoma peritonei was only directed towards palliation and delaying the lethal outcome that appeared to be inevitable [9]. Based on better understanding of the unique biology of this disease, with its predictable distribution limited to peritoneal surfaces, a more aggressive approach has been pursued [1, 10, 11]. The introduction of cytoreductive surgery and intraperitoneal chemotherapy has resulted in a significant number of long-term survivors [13]. This has stimulated greater interest in this rare condition because the experience gained here may be of use in the treatment of other malignancies, such as gastric, ovarian and colon cancer; in these diseases, transperitoneal cancer dissemination remains an important cause of surgical treatment failure.

In earlier analyses, we demonstrated that recurrence after cytoreduction and intraperitoneal chemotherapy is related to incomplete cytoreduction and to high-grade mucinous tumour [4]. Incomplete cytoreduction results in recurrence in the area of residual tumour, presumably because intraperitoneally delivered drugs will not diffuse sufficiently into residual tumour to reach effective tissue concentrations. High-grade adenocarcinoma will frequently recur as metastatic disease which is not influenced by the intraperitoneal approach. These may be called predictable recurrences and, assuming that a maximal effort at cytoreduction was made, the only way to improve results is better patient selection.

Recurrence after complete cytoreduction in patients with grade 1 pseudomyxoma represents failure of the intraperitoneal chemotherapy treatment of this disease. With a goal of improving our understanding of the mechanisms behind these failures, the pattern of recurrence was studied in patients with grade 1 pseudomyxoma peritonei after complete cytoreduction and early postoperative chemotherapy. Mechanisms for treatment failure to be considered include: unexpected change to a more aggressive tumour biology; unobserved incompleteness of cytoreduction; insufficient exposure of residual tumour to intraperitoneal chemotherapy and resistance to chemotherapy.

Recurrence may arise because the original diagnosis was not correct and regional treatments were given to a high-grade adenocarcinoma. Alternatively, recurrence may come about because dedifferentiation had taken place, with change in the tumour biology. A continuing problem is heterogeneity with variation in histology in different parts of the total tumour mass. This sampling error has been frequently observed and leads to incorrect prognostication [14, 16]. In this series, recurrence as a higher grade mucinous adenocarcinoma took place in four of the 32 cases. The majority of cases recurred again in the abdominal cavity as grade 1 pseudomyxoma.

Cytoreductive surgery is conceptually distinct from classical oncological surgery. Obviously *en bloc* resection is not possible; rather, the objective is the removal of cancerous tissue to less than the human eye can see. It is undoubtedly true that the completeness of cytoreduction is not the same in the different peritonectomy procedures. This may be an important factor explaining some differences in the distribution of tumour observed at recurrence as compared to the original presentation. The peritonectomies of the left subhepatic/lesser omentum area are technically the most difficult with the greatest likelihood of unobserved and consequently unresected tumour. There was a predominance of recurrences in this area. Alternatively, the peritonectomies of the undersurface of the diaphragms and of the small pelvis are technically easier and a more successful cytoreduction is possible. It is not surprising that few major tumour recurrences were observed in these areas.

Another area of interest in this respect is the small bowel. The surface of the small bowel showed very limited involvement at presentation, but, was far more involved at recurrence. Tumour from the visceral peritoneal surface of the small bowel can only be partially resected with minimal electrosurgical dissection. By necessity, more tumour remains behind than with a complete stripping of a more uniform parietal peritoneal surface.

The finding that recurrence at the laparotomy site was observed more frequently in patients who also presented with pseudomyxoma peritonei in the abdominal incision suggests that incomplete excision is responsible. It is our impression that this may be related to preservation of the umbilicus, when excising a tumour in a laparotomy scar. As a result of this study, the umbilicus and a margin of normal tissue along the entire old abdominal incision is performed as part of the cytoreductive surgery.

From the pattern of recurrences, a strong impression arises that insufficient exposure of mucinous tumour to intraperitoneal chemotherapy plays a major role and has several causes.

Entrapment.

Tumour at surgical wound sites was the dominant location for recurrence in these patients. In all but 3 patients there was major tumour progression either at the laparotomy site, or at one of the intraperitoneal suture lines. This observation strongly supports the hypothesis that tumour cells are entrapped in surgical wound sites. This factor may also play a role in development of large tumour recurrences on small bowel, which is often extensively traumatised by lysis of adhesions and by cytoreduction. Also, there are experimental data supporting that tumour cells entrapped in suture lines are inaccessible for intraperitoneal chemotherapy [5, 6]. If intraperitoneal chemotherapy is given in the postoperative period, after closure of the abdominal incision and after bowel suture lines are constructed, entrapped tumour cells will not be exposed to the drugs.

Unequal distribution of the intraperitoneal chemotherapy.

The early postoperative intraperitoneal chemotherapy used in the patients in this study was aimed at destroying residual mucinous tumour cells. However, the technique of postoperative infusion of 1 litre of fluid in the peritoneal cavity may not result in even distribution over the whole abdomen and pelvis.

The fluid tends to sit in the lower abdomen and is moved by the activity of the diaphragm up along the paracolic gutters to the subdiaphragmatic spaces. As a consequence, pelvis and subdiaphragmatic areas tend to be fully exposed, while the subhepatic area and the surfaces between the small bowel loops tend to be poorly exposed. This has been confirmed by repeated observation of the staining of peritoneal surfaces with dye, which was added to the infusate during closed intra-operative intraperitoneal chemotherapy. The areas of limited staining match up with the areas most affected by recurrence: the subhepatic/lesser omentum area and the surfaces of small bowel and small bowel mesentery (unpublished data).

Pleural metastases.

An important observation that requires adjustment of therapy for future patients was the development of pleural metastases exclusively in patients in whom the pleural cavity had been entered during cytoreduction. Apparently, the pleural environment is just as supportive of mucinous tumour cells as is the peritoneal cavity. This observation suggests that tumour cells present in the peritoneum during surgery were disseminated into the pleural space. More aggressive tumour under the diaphragm in these patients may also have contributed to spread to the pleura. Of course, tumour cells entrapped in the pleura space are not exposed to intraperitoneal chemotherapy.

Relative resistance against 5-fluorouracil and mitomycin is clearly present in almost all low-grade adenocarcinomas. However, the pattern of recurrence with its reduced presence of tumour in areas fully exposed to the drugs and increased tumour presence in areas that were inaccessible to the drugs, suggests that absolute resistance was not a prominent cause of recurrence in these tumours.

The aim of surgery for pseudomyxoma peritonei must be to remove all tumour down to the millimetre level so that intraperitoneal chemotherapy can reach an effective tissue concentration by diffusion. Further reduction with current technology of residual tumour on the small bowel by more aggressive surgery is, in our view, not feasible. Further small bowel dissection would increase the risk of major morbidity. However, some changes in surgical approach seem appropriate. Based on these observations, the umbilicus is usually included in the resection. In view of the recurrences found at suture lines that we made during earlier operations, the areas of high probability for entrapment are being resected, such as the caecum after appendectomy for pseudomyxoma, or a prior ileocolic anastomosis when gross mucinous ascites was present in the abdomen.

The alarming frequency of pleural spread after opening the diaphragm (75%) suggests that it is important to try and keep the diaphragms intact during subdiaphragmatic peritonectomy. What to do in a case of dense involvement of the tendinous part of the diaphragms presents a dilemma. The choice between resection with entering the pleura or leaving tumour behind remains difficult.

Improvement of treatment in pseudomyxoma peritonei patients depends, in our opinion, largely on the development of more effective intraperitoneal chemotherapy. A new strategy that is currently being pursued is heated intra-operative intraperitoneal chemotherapy, using non-cell cycle-dependent drugs. This new timing of chemotherapy delivery may overcome some of the problems of tumour cell entrapment, for it is given before suture lines are made and before the fascia of the abdominal wall is closed. If intra-operative intraperitoneal chemotherapy is given with the laparotomy wound still open, the surgeon may contribute to more adequate distribution of the infusate over all abdominal surfaces by manually separating structures repetitively. The addition of hyperthermia to drugs may improve diffusion into residual tumour cells and, therefore, improve cell kill.

A second improvement may result from more intensive follow-up and repeat therapy. The observation that the majority of cases remain low-grade when recurring means that a second cytoreduction and intraperitoneal chemotherapy is possible. With this in mind, it is obviously important to identify patients with recurrence early, before a renewed spread of tumour over the complete abdomen has taken place. Tumour markers plus abdominal and pelvic CT-scans are sensitive and convenient guides to early diagnosis of recurrence. Tumour marker directed second-look surgery has, in our opinion, a firm place in the management of these patients.

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