Recurrence of pseudomyxoma peritonei after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Background: Pseudomyxoma peritonei (PMP) is a rare clinical condition characterized by mucinous ascites, typically related to appendiceal or ovarian tumours. Current standard treatment involves cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), but recurrences occur in 20–30 per cent of patients. The aim of this study was to define the timing and patterns of recurrence to provide a basis for modifying follow-up of these patients.

Methods: This observational study examined a prospectively developed multicentre national database (RENAPE working group) to identify patients with recurrence after optimal CRS and HIPEC for PMP. Postoperative complications, long-term outcomes and potential prognostic factors were evaluated.

Results: Of 1411 patients with proven PMP, 948 were identified who had undergone curative CRS and HIPEC. Among these patients, 229 first recurrences (24⋅2 per cent) were identified: 196 (20⋅7 per cent) occurred within the first 5 years (early recurrence) and 30 (3⋅2 per cent) occurred between 5 and 10 years. Three patients developed a first recurrence more than 10 years after the original treatment. The mean(s.d.) time to first recurrence was 2⋅36(2⋅21) years. Preoperative chemotherapy and high-grade pathology were significant factors for early recurrence. Overall survival for the entire group was 77⋅9 and 63⋅1 per cent at 5 and 10 years respectively. The principal site of recurrence was the peritoneum.

Conclusion: Recurrence of PMP was rare after 5 years and exceptional after 10 years.

*Members of the RENAPE Network are co-authors of this study and can be found under the heading Collaborators.

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Introduction

Pseudomyxoma peritonei (PMP) is a condition characterized by mucinous ascites, which leads to abdominal distension, pain, bowel obstruction and anorexia. It results from extensive mucin secretion by a primary tumour in the peritoneal cavity, most commonly originating in the appendix or ovary1, but occasionally from mucinous colorectal tumours1–3. Treatment for PMP has evolved over the past two decades, and now ideally involves complete cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS plus HIPEC). When performed in a high-volume centre, this combination can achieve overall survival (OS) rates of over 60 per cent at 10 years4, although, PMP being a heterogeneous disease, survival varies according to disease aggressiveness, primary pathology and the extent of tumour removal during the initial surgery5,6. Surveillance is warranted as patients who develop a recurrence may be amenable to repeat surgery, leading to extended survival7,8.

Patterns of recurrence in these slow-growing tumours are currently not well defined, and optimal surveillance has not been standardized. The aim of the present study was
Patients with histologically proven PMP
\( n = 1411 \)

Curative surgery undertaken
\( n = 1017 \)

Adequate data on recurrence
\( n = 948 \)

Sufficient long-term follow-up
\( n = 493 \)

Only first CRS and HIPEC considered
\( n = 425 \)

Patients with at least 10 years of follow-up or known recurrence
\( n = 262 \)

No recurrence after 10 years of follow-up
\( n = 39 \)

Early recurrence (within 5 years of follow-up)
\( n = 196 \)

Late recurrence (at 5–10 years of follow-up)
\( n = 30 \)

Recurrence after 10 years of follow-up (excluded from analysis)
\( n = 3 \)

Fig. 1 Flow chart of patient selection and study groups selected for analysis of pseudomyxoma peritonei (PMP). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

Methods

A prospective multicentre database (RENAPE working group) was used to identify all patients who had undergone surgery for PMP between 1993 and 2015. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The diagnosis of PMP was based on preoperative CT, operative findings and pathological confirmation. Preoperative data included patient demographics, origin of the primary tumour, number and type of previous interventions, and the use and type of systemic neoadjuvant therapy. Operative data included the Peritoneal Cancer Index (PCI), calculated during the operation, size of residual lesions, duration of the surgery and the type of HIPEC used. Pathological analyses included histological grade (according to the WHO 2010 classification) and lymph node involvement. Tumours were graded as described by Carr. Postoperative systemic treatments, long-term survival and recurrence were recorded.

All patients analysed were treated with optimal CRS, and HIPEC was administered with either a closed or an open technique, as described previously. Patients were excluded from analysis when they underwent a palliative debulking procedure. The quality of CRS was defined according to the Sugarbaker completeness of cytoreduction (CC) score: CC-0, no macroscopic residual tumour; CC-1, residual tumour smaller than 2.5 mm; CC-2, residual tumour between 2.5 and 25 mm; and CC-3, residual tumour greater than 25 mm. When the score was CC-0 or CC-1, the CRS was considered complete. To achieve optimal CRS, patients underwent multiple peritonectomies and visceral resection of involved organs. For patients who had multiple CRS + HIPEC treatments, only the first treatment was included in the analysis. Patients were excluded when the follow-up was insufficient for this analysis (less than 5 years).

Patients were followed up for recurrence according to the individual institutional guidelines. Follow-up for patients with low-grade tumours tended to include physical examination, estimation of cancer markers, and CT or MRI 6 months after surgery and every year up to 10 years. Follow-up for patients with high-grade tumours was generally followed in a manner similar to evaluate long-term recurrence patterns in PMP treated with optimal CRS + HIPEC, to provide a better definition of the follow-up required after apparent complete disease eradication.
to protocols used for colorectal adenocarcinoma with physical examination, estimation of cancer markers and CT every 3 months in the first 2 years, every 6 months for the next 3 years, and then annually for life. Recurrences were confirmed with CT, abdominal MRI or PET, according to previously published criteria. When the diagnosis could not be ascertained with radiology, exploratory laparoscopy with biopsy was performed to confirm recurrence.

Three patient groups were created for comparative purposes: patients with no recurrence after follow-up of at least 10 years, those with early recurrence within 5 years, and those with late recurrence between 5 and 10 years. Recurrences at more than 10 years of follow-up were excluded from the statistical analysis.

**Table 1** Sites and time to recurrence in patients with recurrent pseudomyxoma peritonei

| Type of recurrence       | All recurrences (n = 226)* | Early recurrence (n = 196) | Late recurrence (n = 30)* | P‡ |
|--------------------------|-----------------------------|-----------------------------|---------------------------|----|
| Peritoneal               | 148 of 225 (65.8)           | 129 (65.8)                  | 19 of 29 (66)             | 0.331 |
| Extraperitoneal†         | 45 of 225 (20.0)            | 37 (18.9)                   | 8 of 29 (28)              |     |
| Both                     | 32 of 225 (14.2)            | 30 (13.5)                   | 2 of 29 (7)               |     |
| Time to recurrence (years) | 2.36 (2–21)               | 1.63 (1–15)                 | 7.15 (1–30)               |     |
| Median (range)           | 1.53 (0.11–9–91)           | 1.24 (0.11–4–93)            | 6.96 (5.14–9–91)          |     |

Values in parentheses are percentages unless indicated otherwise. *Data on type of recurrence were missing for one patient. †Extraperitoneal sites included liver, lung, lymph node, pleura and bone. §χ² test.

**Table 2** Clinicopathological and morbidity characteristics of patients with pseudomyxoma peritonei

| No. of patients* | No recurrence (n = 259) | Early recurrence (n = 196) | Late recurrence (n = 30) | P§ |
|------------------|-------------------------|---------------------------|--------------------------|----|
| Age at surgery (years)† | 53 (9 (11–6)           | 51.6 (9.7)                 | 54.9 (11.8)               | 0.052† |
| Sex ratio (F : M) | 153 : 106               | 22 : 11                    | 116 : 80                  | 0.405 |
| Site of primary lesion | 221 of 233 (94–8)      | 29 of 30 (97)              | 163 of 173 (94–2)         | 0.000 |
| Appendix          | 9 of 233 (3–9)          | 1 of 30 (3)                | 7 of 173 (4–0)            | 1 (3)  |
| Other             | 3 of 233 (1–3)          | 0 of 30 (0)                | 3 of 173 (1–7)            | 0 (0)  |
| Previous surgery  |                         |                           |                          |     |
| Laparoscopy       | 87 (33–6)               | 10 (30)                    | 68 (34–7)                 | 0 (30)  |
| Cytoreduction     | 66 (25–5)               | 7 (21)                     | 48 (24–5)                 | 11 (37)  |
| Preoperative chemotherapy | 90 (34–7)           | 13 (39)                    | 69 (33–2)                 | 8 (27)  |
| PCI†              | 23 (2–36)               | 11 (3–36)                  | 24 (2–36)                 | 16 (3–33)  |
| Duration of surgery (min):§ | 480 (90–875)       | 420 (150–690)              | 480 (95–875)              | 420 (90–765) |
| CC score          |                         |                           |                          |     |
| CC-0              | 201 (77–6)              | 28 (85)                    | 149 (76–0)                | 24 (80)  |
| CC-1              | 58 (22–4)               | 5 (15)                     | 47 (24–0)                 | 6 (20)  |
| WHO classification |                         |                           |                          |     |
| Low grade         | 62 of 199 (31–2)        | 15 of 25 (60)              | 33 of 147 (22–4)          | 14 of 27 (52) |
| High grade        | 137 of 199 (68–6)       | 10 of 25 (40)              | 114 of 147 (77–6)         | 13 of 27 (48) |
| Postoperative chemotherapy | 36 of 258 (14–0)     | 2 (6)                      | 32 (16–3)                 | 2 of 29 (7) |
| Major complications | 127 of 257 (49–4)    | 15 (45)                    | 96 of 194 (49–5)          | 16 (53)  |

*With percentages in parentheses unless indicated otherwise values are †mean(s.d.) and §median (range). PCI, Peritoneal Cancer Index; CC, completeness of cytoreduction. ¶χ² test. Fisher's exact test, except ¶ANOVA or Kruskal–Wallis test.

**Table 3** Site of recurrence according to pathological tumour grade

| All patients | Low grade (n = 46) | High grade (n = 127) | P† |
|--------------|-------------------|---------------------|----|
| Type of recurrence |                   |                     |    |
| Peritoneal    | 109 (63–0)        | 28 (61)             | 81 (63–8) |
| Extraperitoneal | 37 (21–4)         | 12 (26)             | 25 (19–7) |
| Both          | 27 (15–6)         | 6 (13)              | 21 (16–5) |

Values in parentheses are percentages. *Data on type of recurrence were missing for 53 patients. †χ² test.

**Statistical analysis**

All statistical analyses were performed with SAS® 9.3 software (SAS Institute, Cary, North Carolina, USA).
Descriptive data are expressed as mean(s.d.), results for quantitative variables as median (range or 95 per cent c.i.) values, and qualitative data as the numbers with percentages. χ² or Fisher’s exact test was performed to evaluate unpaired data. For paired data, ANOVA was performed. The Kruskal–Wallis test was used when there was non-normality. Post hoc analyses were performed with the Tukey, Games–Howell or Dunn test to identify paired groups with statistically significant differences. Estimates of survival were calculated using the Kaplan–Meier method and compared with the log rank test. Significance was set at $P < 0.050$.

**Results**

Of a total of 1411 PMP treatments during the study period, 394 patients who either underwent incomplete cytoreduction or did not receive HIPEC were excluded. A further 69 patients with missing data for recurrence were also excluded. A total of 948 patients met the inclusion criteria, of whom 229 (24.2 per cent) developed a recurrence (Fig. 1). Among the recurrences, 196 (85.6 per cent) occurred before the 5-year follow-up, 30 (13.1 per cent) between the 5-year and 10-year follow-up, and three (1.3 per cent) after the 10-year follow-up (excluded from the statistical analysis). After optimal CRS + HIPEC, the mean time to first recurrence was 2.36 (2.21) years (Table 1).

Of the three comparator groups created, there were 33 patients with no recurrence after follow-up of at least 10 years, 196 who developed early recurrence within 5 years and 30 who developed late recurrence between 5 and 10 years (Fig. 1).

Patient characteristics are presented in Table 2. In the vast majority of patients (94.8 per cent), PMP was of appendiceal origin. The three patient groups underwent similar numbers of previous surgical treatments. Those with no recurrence after 10 years had a lower rate of preoperative
systemic chemotherapy (18 per cent) than the other two groups (41·5 per cent for early and 28 per cent for late recurrence; \( P = 0·019 \)). Postoperative systemic chemotherapy rates were similar between the groups. The WHO pathological classification of PMP indicated significantly more high-grade disease in the early recurrence group (77·6 per cent) compared with late recurrence (48 per cent) and no recurrence (40 per cent) groups (\( P < 0·001 \)). Intraoperative PCI values were significantly different between no recurrence and early recurrence groups (11 versus 24 respectively; \( P = 0·046 \)).

The mean time to recurrence was 1·63 years in the early recurrence group and 7·15 years in the late recurrence group, but the type of recurrence (peritoneal or extraperitoneal) was not significantly different between groups (Table 1). The peritoneum was the most frequent recurrence site (65·8 per cent for early and 66 per cent for late recurrence). Extraperitoneal sites were implicated in 18·9 per cent of early recurrences and 28 per cent of late recurrences. Both peritoneal and extraperitoneal sites were involved in 15·3 per cent of early recurrences and 7 per cent of late recurrences. Sites of recurrence were not significantly different between the groups when defined by the timing of the recurrence (\( P = 0·331 \)) (Table 1). The organs involved in extraperitoneal recurrence included liver, lung, lymph node, pleura and bone, in descending order of frequency. There was no difference in recurrence site between tumour grades (Table 3).

The entire group had 5- and 10-year OS rates of 77·9 and 63·1 per cent respectively. After excluding patients with no recurrence, to determine survival among patients with recurrence, the 5- and 10-year OS rates were 73·8 and 53·6 per cent respectively (Fig. 2).

When OS rates were analysed according to site of recurrence there was no significant difference in survival among patients with recurrence that occurred within the peritoneum, outside the peritoneum or at both sites (Fig. 3).

The precise timing of recurrences, indicated by the number of recurrences in each 2-month interval, is shown in Fig. 4.

### Discussion

The major finding of this study was the confirmation that about 25 per cent of patients treated with optimal CRS + HIPEC experienced a recurrence. PMP pathology and the use of preoperative chemotherapy were significant prognostic factors for recurrence. Although the mean time to recurrence was nearly 2·5 years, 14·4 per cent of patients (33 of 229) experienced a recurrence after 5 years. The OS rate of patients with a recurrent PMP who underwent a second optimal cytoreduction and HIPEC treatment was similar to that reported previously for patients treated for a first PMP\(^{14}\). The PCI score and site of recurrence did not significantly impact on the timing of recurrence.

The present study focused on patients who underwent optimal CRS + HIPEC. Of the 948 patients treated with this regimen, 229 (24·2 per cent) had a recurrence during follow-up, similar to the 26·8 per cent recurrence rate reported by the Basingstoke group\(^8\) for 712 patients who received optimal CRS + HIPEC. Among recurrences in the present study, 85·6 per cent occurred within 5 years. In contrast, in a large population of patients with colorectal cancer, late recurrences (more than 5 years) following a curative resection accounted for only 4·3 per cent of all recurrences, and late recurrences
were more likely to occur with less aggressive primary tumours.

The largest international PMP registry has defined predictors of poor disease-free survival as: previous systemic chemotherapy, high histopathological grade, major postoperative complications, high PCI, and no HIPEC after CRS. Those markers were consistent with the present results, where patients with aggressive histology (high grade) were more likely to experience early recurrence (before 5 years), and patients with low-grade disease more likely to experience late recurrence.

For most types of peritoneal metastasis, a high intraoperative PCI has been associated with a poor prognosis. This is not always the case, however, according to a Peritoneal Surface Oncology Group International review, in which patients with mucinous disease of the peritoneum were considered to represent a distinct group that exhibited high survival rates, despite a very high PCI. The present results did not show a statistically significant association between the intraoperative PCI and timing of recurrence, although the intraoperative PCI score was greater in the early than in the late recurrence group (24 versus 16 respectively). This may reflect the small sizes of the comparator groups.

Previous systemic chemotherapy is another factor associated with poor prognosis. In the present study, the vast majority (82 per cent, 27 of 33) of patients with no recurrence after 10 years had not received preoperative chemotherapy. The proportion of patients who had received preoperative chemotherapy was significantly higher in the early recurrence than in the late recurrence group (41·5 per cent). This might reflect a more aggressive pathology or a higher tumour burden that led the physician to determine a need for chemotherapy before surgery. Alternatively, the association between early recurrence and preoperative chemotherapy could be that chemoresistant tumour cell clones were selectively spared after systemic chemotherapy. This possibility suggests that the timing and the route of administration of chemotherapy may be important factors in preventing chemoresistant cell selection.

The location of recurrence was not influenced by the timing of recurrence. Recurrences were exclusively peritoneal in approximately two-thirds of each group. Only about one-quarter of patients in the early and late recurrence groups had an isolated extraperitoneal recurrence. A recent study reported that, in patients treated with curative intent for a first PMP recurrence after optimal CRS + HIPEC, the 5-year OS rate was 83 per cent, compared with only 27 per cent in patients with extensive disease not amenable to optimal CRS + HIPEC. The present results were consistent with those from that study: among all patients who had a recurrence, 5- and 10-year OS rates were 73·8 and 53·6 per cent respectively, compared with their reported rates of 68 and 61 per cent. These findings emphasize the need for early detection of recurrence, as a good outcome is achievable when recurrent disease is resectable.

The ideal follow-up regimen after CRS + HIPEC for PMP has not been standardized. Exposure to radiation, as a result of multiple CT scans, has been shown to be associated with an increased risk of secondary malignancy, particularly in younger patients. Abdominal MRI can provide adequate detection of peritoneal mucinous accumulations, and the results seemed better than those achieved with CT in some centres. Abdominal MRI may be an alternative to CT for follow-up imaging, particularly in patients with low-grade PMP, in whom the risk of extraperitoneal recurrence is low.

Most recurrences in the present series occurred within the first 2 years after treatment, supporting the need for frequent surveillance during this interval. This study has limitations. The inclusion period was long (23 years, from 1993 to 2015) and survival has improved over time as techniques have been modified. In 1992, few centres performed CRS. Follow-up methods have also changed, such as the inclusion of MRI. The greater sensitivity of MRI in detecting recurrence may have affected the apparent distribution of recurrences between the follow-up time intervals defined in this study. HIPEC regimens and exposure times varied in different centres. Lack of standardization may have been associated with variations in patterns of recurrence between centres that could not be identified. As with all retrospective designs, sample size and missing data may have introduced bias.

The outcomes of CRS + HIPEC for PMP are improving and encouraging, particularly after optimal resection of the disease. As one in four patients experienced recurrence and more than 10 per cent of recurrences occurred after 5 years of follow-up, it seems appropriate to follow these patients for at least 10 years. The ideal surveillance regimen remains to be defined, but the present results support combinations of CT and abdominal MRI for at least 10 years, conducted more frequently in the first 2 years, and focusing on abdominal recurrences that might be amenable to repeat surgery.

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