Pseudomyxoma peritonei treated with complete resection and immediate intraperitoneal chemotherapy

Dominique ELIAS (1), Stanislas LAURENT (1), Samy ANTOUN (2), Pierre DUVILLARD (3), Michel DUCREUX (4), Marc POCARD (1), Philippe LASSER (1)


SUMMARY

Aim — Pseudomyxoma peritonei remains a fatal disease. This clinical pathological entity based on the presence of mucin includes different prognostic groups. Complete resection of macroscopic lesions, combined with immediate intraperitoneal chemotherapy to treat remnant infra-millimetric disease, might improve survival. The aim of this prospective study was to evaluate this treatment strategy.

Methods — Thirty-six patients with pseudomyxoma peritonei under went resection of supra-millimetric lesions then were given either early postoperative intraperitoneal chemotherapy (5 days) (before January 1996) or intraoperative chemohyperthermia treatment (after January 1996). During this same period, only partial resection of the macroscopic lesion was possible in 15 patients; these patients were not given peritoneal chemotherapy.

Results — Postoperative mortality was 13.8% (n = 5), including 2 deaths not specifically due to the procedure. Morbidity, including severe and non-severe complications was 44%. After a mean follow-up of 48 months, the overall 5-years survival rate was 66%, and disease-free survival rate was 55% (including the postoperative deaths). The main prognostic factor in this series was the pathological grading; 5-years survival was 74% for grade 1 tumors versus 54% for grades 2-3 (P = 0.03).

Conclusion — The main prognostic factor of the pseudomyxoma peritonei, after the completeness of the resection, is the pathological grading. The addition of an intraperitoneal chemohyperthermia improves long-term survival of grades 2-3 tumors and perhaps that of grade 1 (agreement of experts). This treatment is more easily performed, more well-tolerated, and more efficient when performed early.


RÉSUMÉ

Pseudomyxomes péritonéaux traités par exérèse complète et chimiothérapie intrapéritonéale immédiate

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Objectif — Le pseudomyxome péritonal est une entité clinico-pathologique basée sur la présence de mucine et qui recouvre des formes évolutives différentes mais toujours fatales. L’exérèse complète des lésions macroscopiques combinée à une chimiothérapie intrapéritonéale immédiate pour traiter la maladie infra-millimétrique résiduelle est une nouvelle thérapeutique susceptible d’en améliorer la survie. L’objectif de cette étude prospective était d’évaluer ce traitement.

Méthodes — Trente-six malades ont été traités par résection chirurgicale des lésions supra-millimétriques et, soit par une chimiothérapie intra-péritonéale postopératoire immédiate pendant une durée de 5 jours (avant janvier 1996), soit par une chimio-hyperthermie intrapéritonéale peropératoire (après janvier 1996). Durant la même période, 15 autres malades n’ont pu être traités que par exérèse incomplète sans chimiothérapie intrapéritonéale.

Résultats — La mortalité opératoire a été de 13,8 % (n = 5), mais 2 décès n’étaient pas spécifiquement imputables à la procédure. La morbidité a été de 44 %, incluant aussi bien les complications majeures que mineures. Après un recul moyen de 48 mois, la survie globale à 5 ans était de 66 % (mortalité postopératoire incluse), et la survie sans récidive de 55 %. Le principal facteur pronostique dans cette série a été le grade histologique du pseudomyxome : survie à 5 ans de 74 % pour les tumeurs de grade 1 et de 54 % pour les tumeurs de grades 2 et 3 (P = 0.05).

Conclusion — Le principal facteur pronostique des pseudomyxomes péritonéaux, après l’exérèse complète des lésions, est le grade histologique. L’ajout d’une chimio-hyperthermie intrapéritonéale améliore la survie des tumeurs de grades 2-3 et peut-être celle des tumeurs de grade 1 (accord d’experts). Ce traitement est d’autant plus simple, mieux supporté et d’autant plus efficace que le malade est traité précocement.

Pseudomyxoma peritonei (PMP) is a rare clinical and poorly understood pathological entity characterized histologically by the presence of a predominant mucin component. Clinical expression ranges from benign disease to fatal malignancy. Appropriate treatment is difficult to establish due to the small number of patients, possible confusion between appendicular or ovarian disease, the different grades of malignancy, and the different treatment protocols proposed to date (abstention, extensive resection, heated intraperitoneal chemotherapy, symptomatic surgery as requested).

Dissatisfied with the poor results obtained after repeated surgery for incomplete resection, we conducted a prospective
Patients

Between January 1994 and January 2001, we attempted to achieve cure in 51 patients with PMP using a treatment protocol combining macroscopically complete cytoreductive surgery and perioperative chemotherapy [IPIC (1994-1995) or HIIC (1996-2000)]. During this period, cytoreductive surgery was considered complete in 36 patients and incomplete in 12 (as expected preoperatively in 6 of them). At laparotomy, tumor reduction was found to be impossible in 3 patients. The prospective series thus included 36 patients who underwent complete cytoreductive surgery and perioperative chemotherapy (IPIC or HIIC).

The immediate intraperitoneal chemotherapy was delivered with the IPIC protocol at the beginning of our experience then with the HIIC protocol. Modalities of these local treatments varied over the 7 years experience and are described in table I. Retrospectively, we considered that the patients who had had the IPIC protocol (without heated chemotherapy), or were included in the first HIIC trial designed to study the pharmacokinetics of heated oxaliplatin delivered intraperitoneally, had not undergone the most optimal procedure. IPIC was used for 4 patients, HIIC followed by IPIC for 9, and HIIC for 23 (including 3 in the first HIIC trial and 6 in the first part of the second HIIC trial). Fourteen patients were thus considered to have received optimal treatment defined as follows: HIIC delivered via a closed circuit with the abdomen held open by upward traction on the skin, heating to 42.44 °C, intraperitoneal infusion of oxaliplatin (460 mg/m² in 2 L/m² 5% dextrose for 30 min) after intravenous infusion of 5-fluorouracil (400 mg/m²) and folate (20 mg/m²) [6].

The histology grades described by Ronnett et al. [7] (table II) were used.

Methods

The extent of PMP dissemination was described in detail at the beginning of the surgical procedure using the scoring system proposed by Sugarbaker [4] (figure 1). This system assigns a score of 0 to 3 for 13 regions of the abdomen giving a total score ranging from 1 to 39.

Surgery was performed to remove or destroy all macroscopically detected disease, such that no nodules greater than 1 to 2 mm were left in place. When residual diseases greater than this defined size was present, no intraperitoneal chemotherapy was delivered. Generally, the peritoneum was completely resected. Tumor nodules or gelatinous deposits measuring 1-5 mm were destroyed by electrodestruction in some cases if they were located on the walls of the small bowel, the stomach, the liver, or the diaphragm. Electrodestruction was achieved by galvanocautery using the "section" setting at maximum power to volatize the seeded tumor deposits. Vapors were extracted with an aspiration device (Airsafe ES2000, Stakhouse, USA) and the tissue surface was immediately cooled with cold saline solution. All infiltrated tissue was resected.

Fig. 1 – Extension of the peritoneal disease (Sugarbaker score) [4]
The peritoneal cavity was divided into 13 regions (with 4 for the small bowel). Each region was scored 0 to 3 (0 = no tumor implant; 1 = implant measuring 0-5 mm; 2 = implants measuring 5-50 mm; 3 = implants measuring > 50 mm or dissemination throughout the entire region). The scores for the 13 regions were added to give an overall score from 1 to 39.

Statistical analysis

Data were recorded prospectively in a dedicated database. Quantitative data were expressed as means ± standard deviation and range. No
patients were lost to follow-up. The chi-square test was used to compare groups with the significance threshold set at 5%. Kaplan-Meier survival curves were plotted and compared with a unifactorial log-rank test.

Results

Intraoperative findings

Pseudomyxoma peritonei involved 11.1 ± 3.6 of the 13 regions of the abdomen (figure 1). The mean dissemination score was 19.6 ± 8.2 (median 21), range: 5-34. Mean operative time was 563 ± 178 min (median 600, range: 285-900). Mean blood loss was 1 856 ± 1 704 mL (median 1 200, range: 200-8 900). Cytoreduction removed all macroscopically detectable malignant tissue (tumor residue = 0 mm) in 23 patients (64%). Residual nodules measuring 1 mm remained in 10 patients (28%) and measuring 2 mm in 3 patients (8%).

On the average, 4.8 ± 2.1 organs were resected (greater omentum, lesser omentum, and peritoneal surfaces excluded) requiring 2.8 ± 2.4 circular digestive anastomoses (median 2, range: 0-7) and 1.4 ± 1.1 lateral closures (median 1, range: 0-3). Suture of the bladder was required in 6 patients, total colectomy in 8 (22%), and remaining short small bowel (< 2 m) in 3. The pleura had to be opened in 8 patients during diaphragmatic peritonectomy but no detectable passage into the thorax occurred.

Postoperative data

Five patients died before discharge (mortality 13.8%). One patient died from cerebral anoxia subsequent to obstruction of the tracheal tube the first night after surgery. The cause of death at day 12 was rupture of a cerebral aneurysm in another patient. Two patients died from cerebral hemorrhage on day 20 and 22 secondary to thrombopenia in one and microangiathrombopathy in the other. The fifth patient died on day 23 from peritoneal mycosis without associated digestive fistula after development of severe neutropenia (neutrophil count < 500).

Morbidity was 44%, including both severe and non-severe complications. Digestive fistulae developed in 8 patients and deep abscesses in 7 (abdominal complication rate 39%), requiring a revision procedure in 6 patients. Forty-four patients

Table I. – The different types of intraperitoneal chemotherapy used successively.

<table>
<thead>
<tr>
<th>Type</th>
<th>Intraperitoneal chemotherapy</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPIC: J1: mitomycin C (10 mg/m²), d2 to d5: 5-FU (1 gr/m²/d)</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>HIIP 1 with mitomycin C 10 mg/m² then IPIC from d2 to d5 with 5-FU 1 gr/m²/d</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>HIIP 1 with mitomycin (20 mg/m²) and cisplatinum (200 mg/m²)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>HIIP 2 with oxaliplatinum from 260 to 410 mg/m², with IV infusion of folinic acid (20 mg /m²) and 5-FU (400 mg/m²)</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>HIIP 2 with oxaliplatin at 460 mg/m² with IV infusion of folinic acid (20 mg /m²) and 5-FU (400 mg/m²)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Total:</td>
<td>36</td>
</tr>
</tbody>
</table>

* IPIC = Immediate postoperative intraperitoneal chemotherapy delivered in a continuous infusion for 5 days after surgery; HIIP 1 = Heated intraoperative intraperitoneal chemotherapy for 60 min at 42 °C using several technical modalities tested successively during the HIIP 1 trial (12); HIIP2: Heated intraoperative intrapertoneal chemotherapy for 30 min with the abdomen held open by upward traction at 42-43 °C delivered within the framework of the HIIP2 trial conducted to establish the pharmacokinetics of intraperitoneal oxaliplatinum given at stepwise increasing doses (13); 5-FU: 5-fluorouracil

Table II. – Pseudomyxoma peritonei: differential histologic patterns between disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis. (PMCA). From Ronnett et al. [7].

<table>
<thead>
<tr>
<th>Origin</th>
<th>DPAM (grade 1)</th>
<th>PMCA (grades 2-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tumor</td>
<td>Mucinous adenoma</td>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Gross aspect</td>
<td>Mucinous ascitis, deposits sparing the small bowel</td>
<td>Carcinomatosis, with zones of infiltration</td>
</tr>
<tr>
<td>Peritoneal tumor</td>
<td>Poor</td>
<td>Moderate to abundant</td>
</tr>
<tr>
<td>Morphology</td>
<td>Abundant extracellular mucin containing simple or very local proliferating mucinous epithelium</td>
<td>Moderate to abundant extracellular mucin containing very proliferative mucinous epithelium or isolated or clustered cancer cells</td>
</tr>
<tr>
<td>Cell atypia</td>
<td>Minimal</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Rare</td>
<td>Few to many</td>
</tr>
<tr>
<td>Invaded lymph nodes</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Invaded neighboring organs</td>
<td>Rare (ovary excepted)</td>
<td>Frequent</td>
</tr>
<tr>
<td>5 year survival</td>
<td>80%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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developed an extra-digestive complication, mainly lung infection
\((n = 12)\), temporary renal failure \((n = 8)\), and aplasia \((grade 3)\)
\((n = 7)\). Intra- and extra-abdominal complications were more
frequent when more than 4 organs were invaded \(P = 0.04\) and
when more than two circular anastomoses were fashioned \(P = 0.03\),
but without a significant correlation with operative time or
extent of blood loss.

Oral feeding could be resumed after 10 days (median).
Median hospital stay was 24 days \(\text{mean} \pm 32.5 \pm 22.1, \text{range:}
14.1-102\) for surviving patients.

**Histology**

There were 22 grade 1 tumors \(\text{diffuse peritoneal adenomucini-
cosis}\), 3 grade 3 \(\text{peritoneal mucinous carcinomatosis}\), and 11
grade 2 \(\text{peritoneal mucinous carcinomatosis with intermediate}
\text{or discordant features}\). Mesenteric lymph nodes were invaded in
6 patients \(17\%\) with grade 2 or 3 tumors. The parenchyma of
resected organs \(\text{ovary, liver, spleen, tail of the pancreas}\) was
free of tumor tissue in all patients.

**Survival**

Median survival was 48 months \(\text{range: 9-104}\). The overall
and disease-free rates of survival at 5 years were 66% and 55%,
respectively. The survival curve exhibited a sharp decline at 3
years followed by a plateau (figure 2). Nine of the 32 patients
\(29\%\) surviving surgery developed recurrent disease. Among
these, 2 of the 5 patients with intraperitoneal recurrence underwent
a second procedure for complete cytoreduction and HIIC \(\text{to date, both remained disease-free during the short}
\text{follow-up}\). The recurrent tumor exhibited a higher histology
grade in 4 patients. The recurrent tumor was extra-abdominal in
4 patients: both pleurae in one patient \(\text{without injury to the}
\text{pleura at the first operation}\), the vaginal resection margin in
another, the obturator foramen in the third, and the lateral aortic
lymph nodes in the fourth. None of these 4 patients achieved
complete remission after recurrence.

At last follow-up, 10 of the 36 patients \(28\%\) had died: 5
during the postoperative period, 4 due to recurrent PMP, and 1
suicide. Among the 26 survivors, 23 \(83\%\) were disease-free.

Five-year survival was better for patients with grade 1 tumors
than those with grade 2 or 3 tumors \(74\% \text{and 54}\%\), respectively,
\(P = 0.05\). Conversely, degree of PMP dissemination, as reflected by
the peritoneal score \(\text{using a cutoff at 20}\), did not appear to
influence prognosis.

**Discussion**

Pseudomyxoma peritonei results from the presence in the
peritoneum of mucus-secreting neoplastic cells, which, when
searched for with an appropriate technique [7], can always be
detected. Patients with PMP develop a characteristic gelatinous
\(\text{or more appropriately mucinous}\) ascitis associated with mucin-
ous and cellular implants on the peritoneum. In our experience,
fluid “gelatinous” ascitis is less common than more compact
tumor formations. The clinical term of “gelatinous disease” should
thus be abandoned because it is rather limiting \(\text{only the first type}
of presentation is included}\) and imprecise \(\text{risk of confusion with}
\text{low-grade malignant ovarian mucinous tumors}\). Thus, the term
PMP includes a group of neoplastic conditions characterized by a
more or less compact accumulation of mucus in the abdomen.
Specific clinical and radiological presentations can be described
but the histological substrata and potential treatments and
prognosis are quite different.

In a large majority of patients \(80\%\), PMP arises from
appendicular disease and not ovarian disease \[8\] although
ovarian seeding, observed in nearly 90% of the female patients
may be misleading \[9\]. PMP is often mistaken for a mucinous
ovarian tumor. Advances in immunohistochemistry and molecu-
lar biology have greatly contributed to the debate concerning the
appendicular or ovarian origin of PMP. The molecular profiles

generally exhibit a colorectal rather than an ovarian pattern \[10\].
Furthermore, K-ras gene mutations and allele losses on chromo-
osomes 18q, 17p, 5q, and 6q, observed in PMP, are not found in
true borderline tumors of the ovary \[11\]. This nosological

distinction is important because of the difference in prognosis:
5-year survival reaches 95-100% for low-grade mucinous tumors
of the ovary, but falls to 75-80% for minimally aggressive PMP
and less than 10% for aggressive PMP \[12\]. In women, very

predominant fluid gelatious ascitis is more suggestive of
peritoneal dissemination of a low-grade malignant mucinous
tumor of the ovary. Molecular biology techniques difficult to
implement in routine practice are required for definite diagnosis.

These patients should thus undergo classical surgery in an
attempt to achieve complete resection, the diagnosis of appendi-
cular PMP then being retained in event of recurrence, although
true PMP can also arise from other organs \(\text{ovary, pancreas,}
\text{colon, bronchi}\) \[8\]. Finally, PMP is difficult to study because it is a
very rare disease; occurring in 2 of 10 000 laparatomies \[13\].

The classical definition of PMP based on the presence of a
large quantity of mucin in the peritoneum is insufficient. Ronnett et
al. \[7, 10, 12\] made an important contribution by identifying 3

distinct histopathological grades of PMP with very different
prognoses. These authors studied the tumor “shell” designated as
the zones of mucinous epithelial cell implantation on peritoneal
surfaces. They described a grading system based on distinctive
features of the shell such as single or multiple layers, cell atypia,
and mitosis index \(\text{table II}\). In clinical practice, there is very little
difference in the prognosis for grade 3 PMP \(\text{mucinous peritoneal}
carcinomatosis}\) and grade 2 PMP \(\text{an intermediary grade}
\text{between grades 1 and 3 where adenomucinosis predominates}
but with associated foci of mucinous adenocarcinoma}\). It might
be useful to group these two grades together.

There is no consensus on standard treatment for PMP and
data in the literature do not lead to clear conclusions. We
nevertheless considered that systemic chemotherapy is currently
ineffective \[14, 15\] and that surgical resection should remain the
fundamental treatment. Unfortunately, most reports have omitted a
detailed description of the tumor mass \(\text{minimal or massive}
PMP}\), its consistency \(\text{from liquid to a solid form}\), the physiologi-
cal status of the patients, the histological grade, or the complete-
ness of the cytoreduction \[14, 16, 17\]. In addition, surgery for
PMP is generally limited to resection of the more accessible
central and gelatinous lesions without removing the peripheral
visceral and parietal peritoneum which is the site of the active
neoplastic process. Consequently, mucin-producing tumor cells
are not destroyed and histological samples are taken from
amorphous paucicellular or even acellular components of the

![Fig. 2 -- Overall and disease free survival rates after complete surgery with immediate intraperitoneal chemotherapy (including the postop-
erative mortality)](image-url)
Our series of patients was homogeneous for PMP resection (complete cytoreduction in all 36 patients) but not for the intraperitoneal chemotherapy protocol (several successive techniques and chemotherapy regimens). This situation resulted from the requirement for strictly controlled therapeutic trials to search for an optimal treatment. Nearly half of our patients treated between 1994 and 2001 were not given what was retrospectively considered optimal treatment. Five postoperative deaths resulted from a cerebral event and thus can be considered to be unrelated to the specific treatment studied here. Treatment-related mortality reported in the literature is to the order of 3-8% [18, 19], a rate similar to our experience over the last four years. Considering only complications requiring a specific invasive treatment [18], the postoperative morbidity in the present series was 27%. Indeed, operative morbidity and mortality are relatively high when curative treatment is attempted for patients with high-grade PMP. The chances of survival remain low for the same reason. Treatment is easier and complications less frequent for patients with minimally disseminated disease whose chances of survival are better [2, 3]. These observations emphasize the importance of diagnosing PMP early and of optimizing first-line treatment. Laparoscopy would be indicated for patients with an unexplained clinical or radiological presentation in order to establish the diagnosis of PMP as early as possible. If the diagnosis of PMP is certain, it would be inappropriate to undertake surgery for incomplete resection since the disease will continue to progress making a second intervention for the inevitable recurrence most difficult.

Two prognostic factors are of prime importance: completeness of the cytoreduction and tumor grade. The largest series reported to date [Sugarbaker [20, 21]] included 550 patients who underwent maximal surgery for complete cytoreduction followed by IPIC or HIIP. Complete cytoreduction (defined as tumor nodules < 2.5 mm in diameter remaining after surgery) was achieved in 79% of the patients. The 5-year survival rate was 20% (despite adjuvant IPIC or HIIP) among patients who had incomplete cytoreduction and continued to fall thereafter. This 5-year survival rate rose to 79% (P = 0.0001) and remained stable among patients who had complete cytoreduction. The overall 5-year survival rate for the 550 patients was only 53% after maximal surgery and IPIC or HIIC. This low rate points out the real gravity of PMP: more than half the patients die within 5 years [14, 16, 17, 20]. Median survival is only 2 years if resection is incomplete [18]. Partial surgery inevitably leads to a second operation (86% of the 56 patients in the Mayo Clinic series) [16]. Complete cytoreduction without intraperitoneal chemotherapy cannot prevent recurrence but can delay its onset (75% clinical recurrence at 2.6 years after complete cytoreduction versus 76% clinical recurrence at 1.9 years after incomplete cytoreduction) [16]. Perioperative intraperitoneal chemotherapy is designed to treat residual microscopic disease. Theoretically, HIIP is more efficacious than IPIC due to the added hyperthermic effect [22] and the fact that all surfaces are flushed when using the procedure considered by Sugarbaker [5, 20] and us as optimal. Strong scientific evidence is however lacking to prove that adjuvant of IPIC or HIIP improves the prognosis in these patients [19]. Nevertheless, the extensive experience reported by Sugarbaker and the quality of the reported results are in favor of improved outcome with this type of treatment. Other reports of smaller series [8, 12, 15, 16, 23] and the results of the present study all point in the same direction, suggesting there is an agreement among experts on this question (strong agreement for grade 2 and 3 tumors, less strong agreement for grade 1 tumors). Consequently, it is currently advisable to propose this type of maximal treatment for all patients capable of tolerating it. Moreover, it would undoubtedly be advisable to propose a second-look during the next three years for all patients or in the event of clinical recurrence: Esquivel and Sugarbaker [24] have demonstrated that 5-year survival reached 74% among 98 patients who underwent a second operation but was only 68% among 223 patients who did not have a second operation.

The histological grade is also an important factor determining survival, as observed in our patients (figure 3) and as was clearly demonstrated by Sugarbaker in a larger series of patients who underwent complete cytoreductive surgery and IPIC or HIIP [20]. In that series, the 5-year survival was 80% among 224 patients with grade 1 PMP and 30% among 162 patients with grade 2 or 3 PMP (P = 0.0001). Histological grade is the only important prognostic factor after completeness of cytoreduction; dissemination in the peritoneal cavity only has a weak effect on prognosis.

In conclusion, in 2002, PMP remains a poorly understood clinical entity grouping together benign to more malignant disease forms with an overall 5-year survival (all types included) of less than 50%. The two principal prognostic factors are completeness of cytoreductive surgery and histological grade. In order to improve prognosis, complete cytoreductive surgery with HIIP should be proposed for patients with grade 2 or 3 tumors and perhaps for patients with grade 1 tumors. This major surgical protocol is easier to perform, better tolerated, and more effective when performed early.

REFERENCES


Fig. 3 – Survival rates according to the pathological grading.


