

## Morbidity and mortality associated with intraperitoneal chemotherapy for Pseudomyxoma peritonei

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Manuscript received December 14, 2001; revised manuscript January 13, 2002

Presented at the 88th Annual Meeting of the North Pacific Surgical Association, Victoria, British Columbia, November 8–11, 2001

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### Abstract

**Background:** Many centers include intraperitoneal chemotherapy for treatment of pseudomyxoma peritonei. This study documented the morbidity of intraperitoneal chemotherapy in a single institution.

**Methods:** A retrospective review of pseudomyxoma peritonei over a 6-year period was undertaken. Treatment, morbidity, and outcome were documented.

**Results:** Eleven patients were identified with an average of 1.9 debulking procedures and 0.8 chemotherapy courses (0.3 complete). Intraperitoneal chemotherapy was not completed in 5 patients because of complications (56%): severe abdominal pain, seizure, neutropenia, and thrombocytopenia (the latter resulted in 1 patient's death). There was no association between incomplete chemotherapy and recurrence. Recurrence was 64% in those without chemotherapy and 44% in those with. Follow-up averaged 26 months and actual 3-year survival was 60%.

**Conclusions:** Intraperitoneal chemotherapeutic morbidity and mortality were 56% and 11%, respectively. Chemotherapy was associated with decreased recurrence. To optimize outcomes, multicenter prospective trials will likely be required to further refine intraperitoneal chemotherapy protocols. © 2002 Excerpta Medica, Inc. All rights reserved.

*Keywords:* Pseudomyxoma peritonei; Intraperitoneal chemotherapy; Morbidity; Dihydropyrimidine dehydrogenase deficiency; Mitomycin C; 5-Fluorouracil

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Pseudomyxoma peritonei is an uncommon condition in which extensive mucinous ascites and implants are believed to result from low-grade appendiceal malignancies. Management of this condition is controversial [1–3]. Tumors treated with multiple debulking procedures alone have 5-year survival rates of 55%, whereas 5-year survival may be increased with the addition of intraperitoneal chemotherapy [4,5]. Intraperitoneal chemotherapeutic strategies typically use mitomycin C and 5-fluorouracil. Many centers employing these approaches now use hyperthermic intraoperative mitomycin C with early postoperative 5-fluorouracil [5,6]. Reported morbidity and mortality for this latter approach is 27% to 48% and 3% to 9%, respectively [6–8]. Our institution incorporated intraperitoneal chemotherapy

without hyperthermia as part of the management strategy for pseudomyxoma peritonei. Little is documented about the morbidity and mortality associated with this approach as the initial group who introduced the method moved onto hyperthermic techniques [9]. The purpose of this study was to assess the outcome of patients with pseudomyxoma peritonei with particular attention to the morbidity of postoperative intraperitoneal chemotherapy in a single tertiary center.

### Methods

From June 1994 to October 2001, 11 patients with pseudomyxoma peritonei were treated. Six had not had previous debulking, whereas the remaining 5 had residual or recurrent disease after operation elsewhere. A total of 20 debulking procedures were performed (including those per-

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Table 1  
Surgical complications

Complication	POD	Treatment	Long-term morbidity
Wound dehiscence	3	Suture under local anesthetic	Died POD18
Wound infection	7	Antibiotics, wound care	No
Pneumothorax	5	Chest tube	No
Ileus	9	TPN, NG, IV fluids	Died POD 18
Small bowel obstruction	11	NG, IV fluids	No
Small bowel obstruction	5	NG, IV fluids, TPN	No
Small bowel obstruction	30	NG, IV fluids	No
Intraoperative bladder injury	0	Primary repair	No

POD = postoperative day; TPN = total parental nutrition; NG = nasogastric suction; IV = intravenous.

formed at other institutions). There were 6 female and 5 male patients with an average age of 52 (range 31 to 82) years. A median of 1.9 cytoreductions (range 1 to 3) and an average of 0.8 intraperitoneal courses were given (0.3 courses were completed on average). Intraperitoneal chemotherapy entailed mitomycin C on postoperative day 1 and 5-fluorouracil on days 2 to 5. Patients then had 5 days of intraperitoneal 5-fluorouracil with mitomycin C given intravenously on day 3 at 4-week intervals, totaling 4 cycles. Incomplete intraperitoneal chemotherapy was defined as any patient not receiving 4 complete cycles. One patient also received radiotherapy and another was treated preoperatively with intravenous chemotherapy. All underwent cytoreduction with parietal and visceral peritonectomy procedures. Teckhoff catheters were inserted at the time of laparotomy in those in whom intraperitoneal chemotherapy was planned. All pathology was reviewed. It is recognized that there are important differences in the degree of histologic differentiation that may be encountered. At one extreme are those with abundant mucin mixed with occasional fragments of relatively normal appearing epithelium, which are designated below as pure pseudomyxoma. At the other extreme are those with mucin admixed with epithelium showing the cytologic features of carcinoma, known below as pseudomyxoma/adenocarcinoma. No patient had extra-abdominal disease. Morbidity was graded according to National Cancer Institutes common toxicity criteria. Institutional approval was obtained to review the outcomes of these patients.

## Results

Review of pathology for the 20 different cytoreductions revealed 5 to have pseudomyxoma and 15 to have the pseudomyxoma/adenocarcinoma variant of the appendiceal malignancy. One patient, who initially had a pseudomyxoma variant, developed a recurrence in which the pseudomyxoma/adenocarcinoma variant was seen. Pathology did not appear to influence outcome in this small patient population (contrary to other observations) [10].

Eight surgical complications occurred in 4 patients (Ta-

ble 1). A minor wound dehiscence, three early postoperative small bowel obstructions (2 patients), prolonged ileus requiring total parental nutrition, intraoperative bladder injury, pneumothorax secondary to central line placement, and a minor wound infection were all documented.

There were five of nine chemotherapy courses that were incomplete. Two patients had their chemotherapy shortened because of severe abdominal pain associated with nausea and vomiting after instillation of 5-fluorouracil (both experienced this side effect during the second cycle at 4 weeks postoperative). After the first instillation of 5-fluorouracil, another patient experienced a grand mal seizure (grade 4) and no further chemotherapy was given. This patient's course was also complicated by a large pleural effusion which was felt to be secondary to a diaphragmatic injury (causing chemotherapy leak and requiring chest tube drainage). Two patients developed neutropenia. One was noted to have neutropenia with a white blood cell count of 2.2 (grade 2) in association with a fever on day 3 of postoperative chemotherapy. The chemotherapy was discontinued with resolution of the fever. This patient went on to have 3 further cycles. In the other, neutropenia (grade 4), thrombocytopenia (grade 4), and stomatitis (grade 2) were documented on postoperative day 13. Subsequently, sepsis, respiratory failure, and disseminated intravascular coagulation developed; on day 19, the patient died owing to insupportable cardiovascular collapse.

In 11 other cytoreductions, no intraperitoneal chemotherapy was planned. One patient had a recurrence and previously had experienced severe abdominal pain. Massive encasement of small bowel with poor survival expectation, ongoing intraabdominal sepsis and patient refusal (2 patients) were also documented reasons for not incorporating chemotherapy. For the remaining 6, no access to intraperitoneal chemotherapy was available as these procedures were performed elsewhere.

Follow-up was complete for all patients. Eleven recurrences/or disease progression occurred in 6 patients. Repeat cytoreductions and intraperitoneal chemotherapy were performed, and 3 of the 6 patients were disease free at last follow-up. There was no increase in disease recurrence in patients with incomplete cytoreduction versus complete cy-

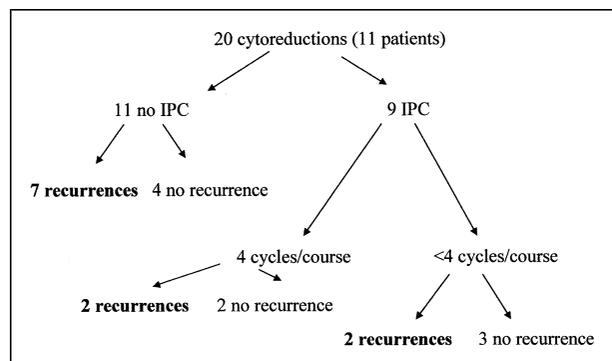


Fig. 1. Recurrence and intraperitoneal chemotherapy factors. IPC = intraperitoneal chemotherapy.

to reduction as long as intraperitoneal chemotherapy was administered. There was a slight tendency for increased recurrence in those who had no chemotherapy with cytoreduction compared with those who received both cytoreduction and intraperitoneal chemotherapy, but statistical significance was not reached ( $P = 0.3$ ; Fig. 1). Follow-up averaged 26 months (range 1 to 85) and actual survival was 60% at 3 years (Fig. 2).

## Comments

It is difficult to define the optimal management for this disease because of factors such as lack of controlled studies, variation in histologic classification, and the rare nature of this entity [4,10]. In addition, the prolonged natural history makes it difficult to determine the impact of therapeutic maneuvers. Centers reporting higher numbers of patients have compared the three techniques: cytoreduction alone, cytoreduction combined with intravenous chemotherapy, and cytoreduction with postoperative intraperitoneal chemotherapy [9]. This analysis seemed to reveal a significant survival advantage for the latter treatment group; however, the analysis was retrospective and compared outcomes from different institutions. Other studies have also suggested an improvement in time to recurrence with the addition of intraperitoneal chemotherapy [11]. Initially, intraperitoneal chemotherapy included mitomycin C with

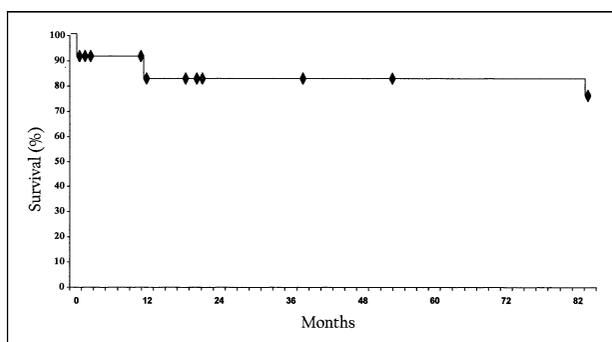


Fig. 2. Kaplan-Meier survival.

5-fluorouracil with subsequent cycles of systemic mitomycin C and intraperitoneal 5-fluorouracil (the protocol followed for the present study) [9]. Modifications have been made to this protocol over the last several years; after cytoreduction, mitomycin C (heated to 44°C) is instilled into the peritoneum with separation of the intraabdominal organs [9]. Patients receive adjuvant intraperitoneal 5-fluorouracil if the pathology reveals mucinous adenocarcinoma or the pseudomyxoma/adenocarcinoma hybrid [8]. Morbidity and mortality associated with this approach is variable depending on institution [6–8].

Hematologic toxicity is most consistently related to intraperitoneal chemotherapy. The main effect of mitomycin C is neutropenia (usually mild), occurring 52% of the time [12]. It is likely that the patient who developed neutropenia on postoperative day 3 was experiencing this toxicity of mitomycin C. 5-Fluorouracil has been implicated as the cause of severe neutropenia with a 66% mortality rate [13]. These patients typically present with fever, neutropenia, and thrombocytopenia on postoperative days 10 to 15 [13]. Obese patients and those with preexisting anemia are thought to be at increased risk for this complication [13]. The patient in the present study who died as a result of hematologic complications developed the toxicity on postoperative day 13. This patient was thought to have a dihydropyrimidine dehydrogenase deficiency, which results in an inability to metabolize 5-fluorouracil with subsequent severe toxicity. This very rare deficiency is known to cause significant morbidity in those treated with this chemotherapeutic agent. She did not have any other risk factors for developing this complication. Of note, mitomycin C resulted in only one of the six complications of intraperitoneal chemotherapy; the majority and most severe complications were 5-fluorouracil-associated.

Hyperthermic intraoperative intraperitoneal chemotherapy has nonhematologic-associated morbidity as well. Intestinal perforations, anastomotic and bile leaks, fistula, bleeding, dehiscence, pancreatitis, and pulmonary embolism have all been documented [7,9]. The rates for this type of morbidity are increased when compared with early postoperative chemotherapy (without hyperthermia) [9]. In the present study, 8 nonhematologic complications occurred in 20 procedures (40%), although none of the above listed morbidities occurred and most were self-limited.

The rationale for hyperthermic intraoperative mitomycin C emerged because of concerns about poor penetrance and non-uniform distribution of intraperitoneal chemotherapy due to dependency and adhesions [9,13–15]. By heating mitomycin C improved penetrance and drug cytotoxicity is thought to occur [15]. The technique involves an additional 90 minutes of operating room time after complete cytoreduction [9]. Given the concern over the increased morbidity with heating and the practical disadvantage of manual drug distribution, some centers have continued using the early postoperative intraperitoneal chemotherapy protocol instead of updating to the newer approach. No data currently exist clearly supporting heated operative over early postoperative intraperitoneal chemother-

apy (or visa versa). Although the present study appears to have increased morbidity of intraperitoneal chemotherapy, most studies do not include abdominal pain as a complication (the most common morbidity leading to incomplete chemotherapy in the current study). Disease recurrence and survival are comparable to those centers using heated intraoperative chemotherapy. An important (and often overlooked) factor in any comparisons is the proportion of patients who did not complete planned intraperitoneal chemotherapy. In the present study, there was no increased recurrence with incomplete intraperitoneal chemotherapy. This is in agreement with what others have found—recurrence has not been found to be related to any intraperitoneal chemotherapy factors (as long as intraperitoneal chemotherapy is given) [9]. There was a tendency to improved outcomes in those receiving both cytoreduction and intraperitoneal chemotherapy. As most of the patients in the current study did receive at least one dose of intraperitoneal chemotherapy, it may be that the initial dose (or doses) are the key to decreasing microscopic residual tumor and ultimately to improving survival. This is an especially important consideration given that most of the major morbidity (and mortality) was associated with 5-fluorouracil, which is most commonly given after mitomycin C. Lack of effect of histologic type likely is an effect of small sample size (1 patient had 3 recurrences, all pseudomyxoma peritonei on pathology).

Overall, the best treatment for pseudomyxoma peritonei remains unclear, yet a decrease in recurrence seems to occur with use of intraperitoneal chemotherapy. Major morbidity and mortality of approaches incorporating intraperitoneal chemotherapy continue to present obstacles in management. Ideally, with multicenter prospective, randomized controlled studies, optimal intraperitoneal chemotherapeutic strategies may be defined. Further refinement of the chemotherapeutic agents, dosage and timing may minimize complications and ultimately further improve survival for this challenging disease.

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