Long-term Survival Following Treatment of Pseudomyxoma Peritonei

An Analysis of Surgical Therapy

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Summary Background Data: Pseudomyxoma peritonei (PMP) is a clinical syndrome with a poorly defined natural history. Relative contributions of tumor biology, patient selection, and the extent of treatment on ultimate outcome are not well characterized.

Methods: Patients treated at the Memorial Sloan-Kettering Cancer Center between 1980 and 2002 with a diagnosis of PMP were identified. Patient characteristics, pathologic features, and details of treatment were analyzed retrospectively.

Results: The 97 patients included in this study underwent a mean 2.2 ± 0.1 operations (range, 1–6). Although complete cytoreduction was achieved in 55% (53/97), disease recurred in 91% (48/53) of patients. The median disease-free interval after complete cytoreduction was 24 months. The median overall survival was 9.8 years and was independently associated with low-grade pathologic subtype ($P < 0.001$) and the ability to achieve complete cytoreduction ($P < 0.001$). Ten-year survival was attained in 21% (20/97) of the patients, of which 90% (18/20) had low-grade pathologic features. At the time of death or completion of follow-up, only 12% (12/97) of the patients were disease free.

Conclusions: Outcome in patients with PMP is strongly associated with tumor biology. Although improved survival is associated with low-grade pathology and tumors amenable to complete cytoreduction, recurrence of PMP is common. Treatment may be beneficial, particularly in controlling symptoms, but absolute cure, defined as a prolonged disease-free state, is uncommon.

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Pseudomyxoma peritonei (PMP) is an uncommon clinical syndrome characterized by the slow and progressive accumulation of peritoneal implants and mucinous ascites. Over time, accumulation of mucin in the peritoneal cavity results in massive symptomatic distension and associated mechanical and functional gastrointestinal obstruction. Inconsistent or imprecise classification of this entity by surgeons, pathologists, and oncologists has caused confusion in the understanding of its natural history. It is now generally thought that PMP arises as the result of neoplastic mucin-secreting cells with low-grade cytologic features disseminating within the peritoneal cavity. In almost all cases, these cells are derived from a ruptured appendiceal neoplasm.

The optimal treatment of patients with PMP remains poorly defined. Although some authors have argued that surgical debulking of PMP should be performed on a selective basis, most agree that patients with PMP are best treated, at least initially, with aggressive local therapy.[1] Recommendations from the literature are contradictory and heavily influenced by observations of dissimilar patient groups. Series frequently have different inclusion criteria that bias their populations towards more or less aggressive extremes of the disease. Studies are further limited by small numbers of patients collected over long periods of time during which treatment paradigms change, by the lack of adequate follow-up data, and by conclusions based on inappropriate endpoints. Sugarbaker,[2] who has published extensively on PMP, and Esquivel and Sugarbaker[3]advocate aggressive cytoreduction with the use of radical peritonectomy procedures followed by intraperitoneal chemotherapy. Reports of this therapy have demonstrated prolonged survival and led some to suggest that it may be curative. Several questions raised from these reports, in combination with the associated morbidity and mortality, have caused others to apply this modality cautiously and selectively.

At the Memorial Sloan-Kettering Cancer Center, the approach to PMP has been to focus primarily on optimal symptom management with surgical therapy. At present, function preserving debulking is performed when possible. Complete cytoreduction is attempted, especially at the first operation, but not at the expense of patients' quality of life. Major organ resection, including gastrectomy or proctec-

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tomy, is performed rarely. Intraperitoneal chemotherapy is used selectively in patients who are able to undergo complete, or near-complete, cytoreduction. The timing of subsequent procedures is driven largely by symptoms. The purpose of this study was to review our institutional experience with PMP, to define its natural history, and to examine the clinical and pathologic features that might aid in clinical decision making. A critical analysis of our results should also allow comparisons to other contrasting therapeutic philosophies.

METHODS

Subjects

Patients treated at the Memorial Sloan-Kettering Cancer Center between 1980 and 2002 with a diagnosis of PMP were identified and analyzed retrospectively. The term pseudomyxoma peritonei was defined clinically on the basis of intraoperative findings as grossly visible, localized, or generalized accumulation of mucin in the peritoneal cavity either lying on and attached to the peritoneal surfaces or incorporated within dense fibrous tissue. Patient data were obtained from clinical records, surgical reports, pathology reports, and pathology slides from prior surgical procedures. Patient characteristics were recorded and listed descriptively.

Histopathologic Analysis

Pathologic materials were reviewed by a single pathologist (JS) to confirm the original diagnoses. Because a large number of cases were referred from outside institutions, the extent or completeness of pathologic sampling could not be determined in all patients. The location of the primary tumor was noted. Samples were evaluated for the grade of both the primary tumor and intraperitoneal implants. The percentage of cells in relation to mucinous material in intraperitoneal implants was determined.

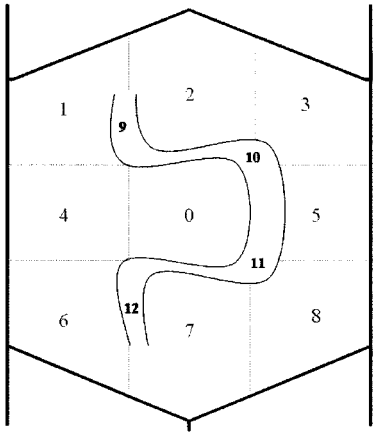
Patients were designated into histopathologic groups based on the work of Ronnett et al.[4] Patients with low-grade primary lesions and well-differentiated intraperitoneal material with low cellularity (0%-10%) were defined as having mucinous adenocarcinoma, low grade. Patients with high-grade primary and mucinous material with high cellularity (>50%) were classified as having mucinous adenocarcinoma, high grade. The 3 intermediate pathologic features included moderately differentiated primary, moderately differentiated mucinous material, and cellularity between 11% and 50%. Patients having 1 of these intermediate features were categorized as mucinous adenocarcinoma, low grade, while those with 2 or more were placed in the mucinous adenocarcinoma, high-grade group.

Operative Details

All patients in the study underwent at least 1 abdominal operation at the Memorial Sloan-Kettering Cancer Center during the course of their disease. The sequence, indications, and time interval between operations were noted for each patient. The nature and duration of patient symptoms prior to each procedure were determined. Procedures performed with palliative intent to explicitly manage patient symptoms or improve quality of life were identified using previously described criteria.[5,6] Although operations classified as nonpalliative seemed to be performed with curative intent to remove tumor, prevent recurrence, or prolong survival time, lack of established and reproducible criteria prevents a more precise designation of surgical intent in these cases.

The extent of each abdominal operation was graded using an extent of surgery score (ESS) based on a modification of Sugarbaker's previous surgery score.[7] This scoring system attempts to objectively quantify the anatomic areas within the abdomen addressed during a surgical procedure in a systematic fashion. Procedures were performed in regions listed 0 through 12. Regions 0 through 8 were associated with specific anatomic structures located within the abdomen and pelvis. Regions 9 through 12 were defined in the small bowel in a proximal-to-distal direction. Figure 1 summarizes the modified ESS scoring system. Radical cytoreduction, defined as an ESS-3 procedure, was characterized by cytoreduction in 5 or more regions of the abdomen often in association with major organ resection.

The completeness of cytoreduction was determined as no gross residual disease, minimal residual disease (90%-99%



Extent of surgery score	Description
0	Biopsy only
1	Exploratory laparotomy with cytoreduction, 1-2 regions
2	Exploratory laparotomy with cytoreduction and resection, 2-5 regions
3	Extensive cytoreduction, >5 regions

FIGURE 1. The extent of surgery score (ESS) is based on the number of abdominal regions involved in the operative procedure. Abdominal regions 0 to 8 are associated with specific anatomic structures located within the abdomen and pelvis. The small bowel is defined sequentially in a proximal to distal direction: region 9 is upper jejunum, region 10 is lower jejunum, region 11 is upper ileum, and region 12 is lower ileum.

cytoreduction), or gross residual disease (<90% cytoreduction). The occurrence of a death or a major operative complication (resulting in reoperation, ICU admission, chronic disability, or death) within 30 days of surgery was noted.

Data Analysis

Data were analyzed using SAS statistical software (release 4.0, SAS Institute Inc, Cary, NC). Data were expressed as percentages in the case of categorical variables and as medians in the case of continuous variables. Means were compared using the Student *t* test, and frequencies were compared using the 2-tailed Fisher exact test or by the χ^2 test, where appropriate. Logistic regression and analysis of variance were performed where indicated. The Kaplan-Meier method was used to determine overall survival from the time of diagnosis of PMP. Disease-free survival after complete cytoreduction and symptom-free survival after any operation were calculated. The univariate association between clinical variables and survival was examined by the log-rank test. Independently associated factors were identified by proportional hazard regression analysis (Cox model). P values less than 0.05 were considered significant.

RESULTS

Patient Presentation

From 1980 to 2002, 97 patients were treated for PMP at the Memorial Sloan-Kettering Cancer Center. All patients had a history of gross mucinous ascites. The mean age at diagnosis was 53 ± 1.5 years (range, 19–84). There was a slight preponderance of women (55%). The mean follow-up was 70 ± 5.5 months (median, 57.5; range, 3–220). Two foreign patients were lost to follow-up after 36 months. One additional patient was lost after 7 years. No patients were eliminated from data analysis.

At presentation, patients most frequently reported progressive abdominal distension (55%, 53/97). A presumed diagnosis of acute appendicitis was made in 20% (20/97) of the patients prior to the diagnosis of PMP. Fourteen percent (14/97) of the patients initially presented with signs and symptoms of gastrointestinal obstruction. The diagnosis of PMP was made in the remaining patients during the evaluation of inguinal hernia (6%, 6/97), nonspecific abdominal pain (3%, 3/97), and occult gastrointestinal bleeding (2%, 2/97).

Clinicopathologic Features

The appendix was grossly determined to be the site of the primary tumor in 97% (94/97) at the time of surgery. Adequate archival pathologic specimens for further pathologic classification were available from 91% (88/97) of the patients. As summarized in Table 1, patients were designated into groups as mucinous adenocarcinoma, low grade in 52% (46/88) and high grade in 48% (42/88). Thirty-one percent (13/42) of the high-grade cases were classified as mucinous adenocarcinoma, high grade, based on 2 or more intermediate features. The grade of intraperitoneal cells was closely associated with the grade of primary tumor ($P < 0.001$). When comparing low- to high-grade groups, there was no significant difference in age ($P = 0.94$), gender ($P = 0.09$), or ovarian involvement in women ($P = 0.62$). Although none of the low-grade patients presented with evidence of nodal or distant metastasis, there was no observed difference in the development of metastasis over the course of their disease ($P = 0.32$).

TABLE 1. Clinicopathologic Features of Patients Identified With PMP*

	Mucinous Adenocarcinoma, Low Grade	Mucinous Adenocarcinoma, High Grade
Number of patients, No.	46	42
Age, mean ± SEM	53.7 ± 2.1	53.8 ± 2.4
Gender		
Male	18 (39)	25 (60)
Female	28 (61)	17 (40)
Grade of primary No., %		
Well	18 (39)	6 (14)
Moderately	5 (11)	12 (29)
Poorly	0 (0)	10 (24)
Unknown	23 (50)	14 (33)
Cellularity of intraperitoneal implants, No., %		
0–10	22 (48)	10 (24)
10–20	18 (39)	17 (40)
20–50	2 (4)	9 (21)
> 50	0 (0)	4 (10)
Unknown	4 (9)	2 (5)
Grade of cells, No., %		
Well	21 (46)	1 (2)
Moderately	19 (41)	20 (48)
Poorly	0 (0)	20 (48)
Unknown	6 (13)	1 (2)
Ovarian involvement, No., %	16 (35)	11 (26)
Nodal or distant metastasis, No.	3 (7)	7 (17)
At presentation	0	3
In follow-up	3	4

*Adequate archival pathologic specimens for complete pathologic classification were available from 91% (88/97) of the patients in this study.

Patient Management

A total of 202 operations were performed in the 97 patients. Patients received an average of 2.2 ± 0.1 operations (range, 1–6). Thirty percent (29/97) had 1, 39% (38/97) had 2, 21% had 3 (20/97), 7% had 4 (7/97), and 3% (3/97) had 5 or more operations. Sufficient information for detailed anal-

ysis of each individual operation was available in 98% (197/202) of the procedures performed.

Symptoms were reported prior to operation in 76% (149/197) of the evaluable procedures. In those patients who were asymptomatic, indications for the procedure often were based on identification of disease on physical examination or radiographic studies. As seen in Figure 2, symptoms were reported less frequently at the time of the second operation ($P = 0.006$) than the first operation. Operations to explicitly manage symptoms were performed with palliative intent in 15% (29/197) of the cases and were most commonly encountered after the third operation ($P = 0.004$). The durability of symptom control tended to decrease after each operation and was significantly shorter after the third ($P < 0.001$) and fourth operations ($P = 0.02$).

Complete resection of all PMP-associated tumor was achieved during at least 1 operation in 55% (53/97) of patients. Complete cytoreduction (Fig. 3) was more commonly associated with the first and second operations (operations 1 and 2 [35%, 53/153] versus operation ≥3 [7%, 3/44], $P < 0.001$). At the initial operations, biopsy alone was performed in 18% (17/97) of patients, and others had an unsuccessful attempt at complete cytoreduction prior to specialty center referral. The ability to achieve complete cytoreduction was not associated with pathologic subtypes (mucinous adenocarcinoma, low grade: 65% [30/46]; versus mucinous adenocarcinoma, high grade: 55% [23/42]; $P =$ 0.32). Of the 53 patients who underwent complete cytoreduction, 91% (48/53) recurred at a median of 24 months (range, 2–103). The disease-free interval was not associated with pathologic subtype ($P = 0.30$), the extent of surgery ($P = 0.92$), or the operation number ($P = 0.83$). Sixty percent (29/48) of the patients who recurred after complete cytoreduction underwent further operations, with 17% (5/29) of the operable patients obtaining complete cytoreduction a second time.

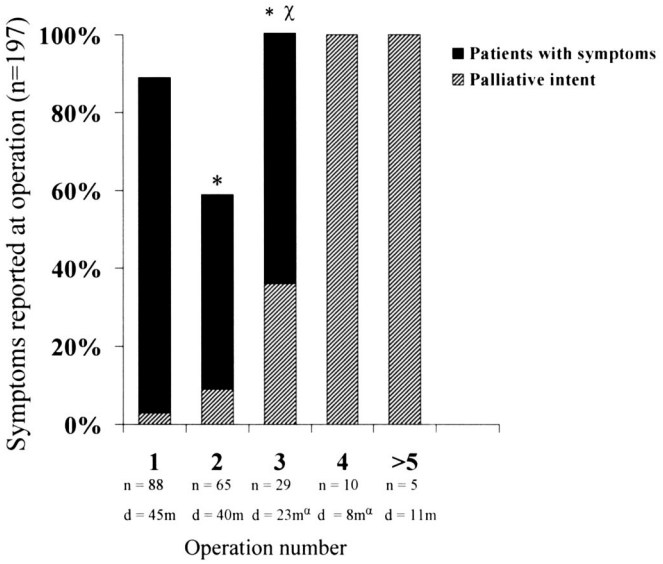


FIGURE 2. The presence of documented symptoms associated with successive operations. The striped section of bar represents operations performed explicitly with palliative intent. * $P < 0.05$ documented symptoms versus prior operation. ^{x} $P < 0.05$ palliative intent versus prior operation. $^{\alpha}$ $P < 0.05$ versus durability of previous operation; d, durability; m, months.

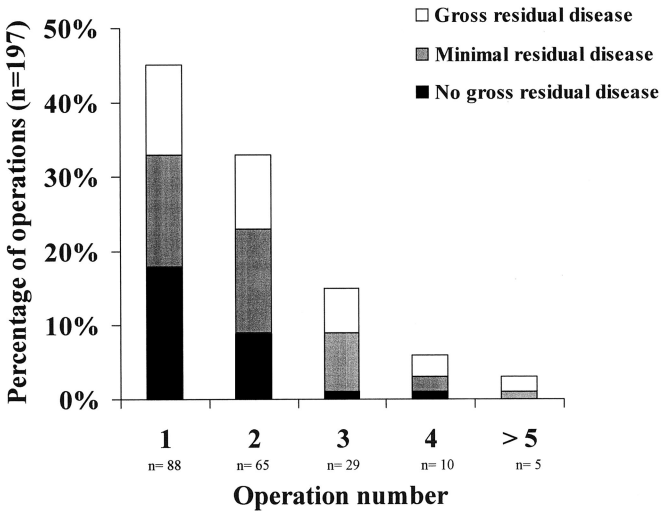


FIGURE 3. Completeness of cytoreduction associated with successive operations. Complete cytoreduction was more common after the first and second operations ($P < 0.001$).

The ESS was 0 in 10% (20/197), 1 in 20% (39/197), 2 in 49% (96/197), and 3 in 21% (42/197) of the procedures. At some time in their clinical history, 39% (38/97) of patients underwent an ESS-3 operation. There was a significant increase in the proportion of ESS-3 procedures performed at the second operation (27%, 17/65; $P = 0.04$) compared with the first. As shown in Figure 4, complete cytoreduction was associated with an ESS-3 procedure in 33% (14/42), an ESS-2 procedure in 34% (33/96), and an ESS-1 procedure in 21% (8/39). There was no difference in the frequency of complete cytoreduction comparing ESS-1, ESS-2, and ESS-3 operations ($P = 0.17$), respectively.

Fifty-eight percent (117/202) of all and 43% (42/97) of the initial operations were performed at the Memorial Sloan-Kettering Cancer Center. At our institution, an ESS-3 procedure was performed in 25% (29/117) of the patients. An adjacent organ resection was performed in 33% (36/117), with patients receiving a small-bowel resection in 15% (17/117), a splenectomy in 9% (10/117), a colectomy in 8% (9/117), a subtotal gastrectomy in 3% (3/117), a hysterectomy in 2% (2/117), and a segmental liver resection in 2% (2/117). A colectomy associated with the formation of a colostomy or

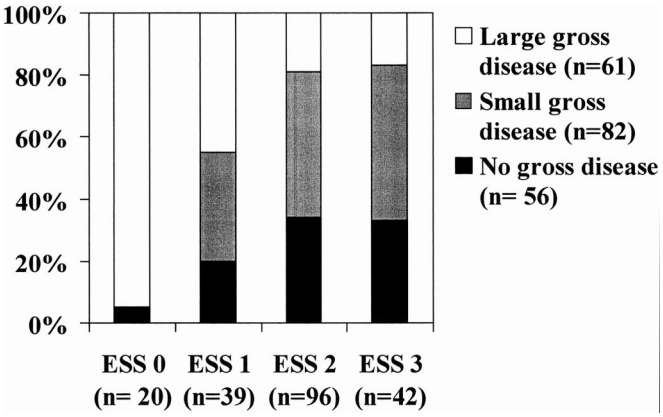


FIGURE 4. Completeness of cytoreduction associated with ESS score.

ileostomy was required in 4% (4/117). A total gastrectomy was performed in a single patient (1%, 1/117).

Fifty-nine percent (59/97) of the patients received systemic chemotherapy at some time during their clinical course. 5-FU was the most commonly used agent (78%, 46/59). Thirty-one percent (30/97) of the patients had a catheter placed for intraperitoneal chemotherapy. A 5-FU based agent was used for intraperitoneal chemotherapy in 67% (20/30) of these patients. Four patients received hyperthermic intraperitoneal chemotherapy. A therapeutic response to chemotherapy was not documented in any patient.

Morbidity and Mortality

The 30-day operative mortality rate was 4% (4/97). Uncontrolled intraabdominal sepsis after ESS-1 operations caused the deaths of 2 patients. Two additional deaths following ESS-3 operations resulted from a pulmonary embolism and a gastric perforation. A major complication resulting in reoperation, ICU admission, or chronic disability was identified after 16% (32/197) of the operations. ESS-3 operations had the highest major complication rate (38%) compared with ESS-1 (18%, 7/39; $P = 0.19$) and ESS-2 procedures (9%, 9/96; $P = 0.003$). A variety of complications was associated with each type of procedure, but a perforated viscus (gastric or colonic) was most commonly associated with an ESS-3 operation ($P = 0.01$). Even though 86% (24/28) of the patients who survived a major complication later had symptoms associated with PMP, an additional operation was performed in only 11% (3/28). One patient had another attempt at complete cytoreduction following a previous unsuccessful operation complicated by prolonged intraabdominal sepsis. The second operation was complicated by the formation of an enterocutaneous fistula. In the remaining 2 patients, the procedure was explicitly performed to palliate severe gastrointestinal obstructive symptoms.

Survival

The median survival of the whole patient population (n = 97) was 9.8 years (range, 0.3 to 18.3 years) from the date of the initial operation. In patients with complete pathologic data, median survival was significantly longer in patients with mucinous adenocarcinoma low grade (12.8 years) versus high grade (4.0 years, $P < 0.001$), as seen in Figure 5. To identify factors important in determining survival, clinical and pathologic factors were analyzed using univariate and multivariate analysis (Table 2). Univariate analysis showed that improved survival also was associated with a clinical history of complete cytoreduction (median, 12.8 years versus 4.2 years, $P < 0.001$), female gender (median, 11.6 years versus 5.1 year, $P < 0.016$), a previous ESS-3 surgery (median, 11.9 years versus 6.6 years, $P = 0.032$), and a prolonged disease-free interval (≥24 months) following complete cytoreduction (median, 12.8 years versus 8.2 years, $P = 0.048$). On multivariate analysis, however, only the designation of low-grade mucinous adenocarcinoma and the history of a complete cytoreduction were independently associated with prolonged survival.

Clinical features of the 10-year survivors (21%, 20/97) are listed in Table 3. Among all patients with PMP, 10-year survival was most likely to be associated with female gender (75%, 15/20; $P = 0.04$) and a pathologic classification of low-grade mucinous adenocarcinoma (90%, 18/20; $P < 0.001$). Although 10-year survivors more frequently had a complete cytoreduction at some time in their clinical course (75%, 15/20; $P = 0.04$), they did not have radical ESS-3 operations at higher rates (50%, 10/20; $P = 0.27$). Due to the advanced age and chronicity of their disease, the precise cause of death in some patients could not be determined adequately in this analysis. At the time of death or the completion of follow-up, however, 23% (6/20) of the 10 year

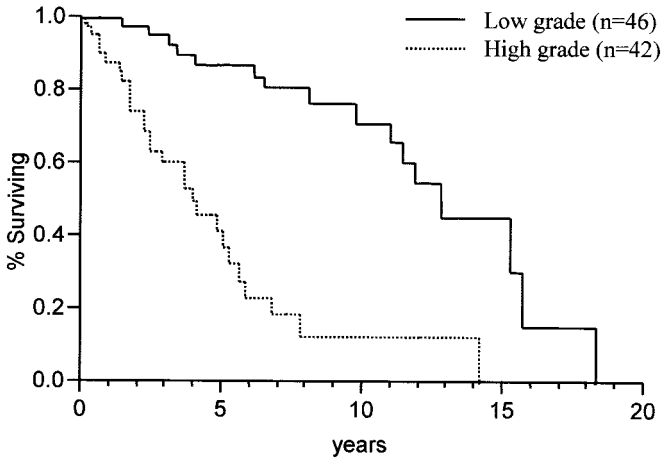


FIGURE 5. Long-term survival associated with pathologic designation ($P < 0.001$).

TABLE 2. Predictors Associated With Prolonged Survival

Variable	No.	Univariate *P* Value	Multivariate	
			Hazard Ratio (CI)	*P* Value
All patients	88			
Low-grade mucinous adenocarcinoma	48	< 0.001	5.1 (2.6–10)	< 0.001
History of complete cytoreduction	53	< 0.001	2.7 (1.4–5.3)	0.003
History of radical ESS-3 surgery	38	0.032	1.7 (0.8–3.1)	0.21 (NS)
Female gender	45	0.016	1.1 (0.8–1.6)	0.38 (NS)
Disease-free interval ≥24 mo	23	0.048	1.1 (0.4–2.1)	0.88 (NS)
Number of operations	88	0.24 (NS)	—	—
Age >55	41	0.35 (NS)	—	—
Systemic chemotherapy	56	0.39 (NS)	—	—
Intraperitoneal chemotherapy	29	0.41 (NS)	—	—

NS indicates not significant.

TABLE 3. Clinical Features of 10-Year Survivors

	Age (y)	Gender	History Radical (ESS-3) Cytoreduction	History of Complete Cytoreduction	Number Operations	Time From Initial Surgery (y)	Status
Low-grade mucinous adenocarcinoma							
1	52	Female	Yes	Yes	2	14.6	NED
2	39	Female	Yes	Yes	4	13.0	NED
3	44	Male	No	Yes	1	12.3	NED
4	68	Female	No	Yes	1	12.2	NED
5	49	Male	Yes	No	2	12.2	AWD
6	54	Female	Yes	Yes	2	12.1	AWD
7	63	Female	Yes	Yes	5	11.5	AWD
8	51	Female	Yes	Yes	4	11.4	AWD
9	56	Female	Yes	No	4	18.3	DWD
10	36	Female	No	No	2	16.5	DWD
11	56	Male	Yes	Yes	2	15.8	DWD
12	72	Female	No	Yes	2	15.3	DOC
13	58	Female	No	Yes	2	12.8	DOC
14	66	Female	Yes	Yes	4	11.9	DWD
15	61	Female	No	No	3	11.5	DWD
16	28	Male	No	Yes	6	11.1	DWD
17	75	Female	No	Yes	3	10.9	DWD
18	60	Female	No	No	3	10.2	DWD
High-grade mucinous adenocarcinoma							
19	52	Female	Yes	Yes	3	12.2	AWD
20	68	Male	No	Yes	2	14.2	DWD

AWD, alive with disease; DOC, died other causes; DWD, died with disease; NED, no evidence of disease.

survivors were disease free. Only 12% (12/97) of the patients in this study were alive with no evidence of disease at the time of last follow-up.

DISCUSSION

Survival is traditionally the most important outcome in cancer treatment.[8] Overall survival signifies death from any cause and represents a discrete, reproducible, and universally recognized measurement. To properly evaluate outcome, however, different endpoints may be more appropriate; disease-free survival is important in the adjuvant setting, progression-free survival in patients with metastatic disease, symptom-free survival in the palliative setting, and event-free survival in the long-term assessment of potentially curative treatments.[9] Without knowing the natural history of a disease process (ie, expected survival without treatment), it is difficult if not impossible to properly design a clinical trial to assess how patients might benefit from treatment.[10] Much of the literature debating the appropriate treatment of PMP is based on overall survival. The value of overall survival as a study end point when considering patients with PMP is limited, as it fails to characterize the impact of disease recurrence, ongoing treatment, and treatment-related toxicity on the quality of life of patients with this insidious, slowly progressive disease. Because of our limited understanding of the natural history of patients with PMP, conclusions based mainly on overall survival should be interpreted with caution.

To overcome some of these limitations in the literature, this study attempts to use previously published standards that may allow more useful comparisons to past reports. In this study, pathology data were analyzed using a schema comparable to that proposed by Sugarbaker's group.[4] Lesions were classified as mucinous adenocarcinoma with a low- or high-grade modifier to reflect the histologic grade of the neoplastic epithelial cells. By definition, the designation of mucinous adenocarcinoma low grade is synonymous to the term *disseminated peritoneal adenomucinosis* as defined in their reports. Although Sugarbaker et al have stated that the term *PMP* should be applied only to benign cases of the disease, others suggest that it should be applied to low-grade malignant conditions as well.[11,12] In this series, the overall median survival was 9.8 years. Patients with mucinous adenocarcinoma, low grade, had an improved overall survival of 12.8 years compared with those with the high-grade variant, where the median survival was 4 years. This report confirms observations made by others that biologic characteristics associated with low-grade forms of PMP are independently associated with improved survival.[4,13]

Support for more aggressive therapy for PMP is often based on comparisons of overall survival in patient groups with diverse or poorly specified pathologic subtypes. Patients with PMP selected for aggressive therapeutic paradigms, such as those advocated by Sugarbaker's group,[2,3,14] by definition only have benign or low-grade lesions. The demonstration of improved survival in a favorable group following maximal therapy does not allow one to properly conclude whether superior results were caused by the biology of the disease process, by good patient selection, or by the specific treatment. A different treatment strategy was used at our institution, based on the selective application of extensive debulking procedures and priority given to function preservation and symptom management. As shown in Figure 6, the overall survival in this series is equivalent to the 5-year and 10-year survival rates of 75% and 68% reported by Esquivel and Sugarbaker[3] and Ronnett et al.[3,13] Although patients from both reports had favorable pathology defined by similar criteria, there are limitations to this type of analysis since specimens were reviewed by different pathologists and the criteria used may not fully reflect unpublished nuances inherent to complete pathologic analysis. This observation, however, does not support the conclusions of authors who propose that radical cytoreduction and adjuvant intraperitoneal treatment are responsible for improved survival in patients with PMP. It suggests that the biology of the disease, rather than the aggressiveness of treatment, ultimately defines outcome.

In this study, improved survival was associated with complete cytoreduction. Patients who were able to undergo complete cytoreduction at some point in their therapy had a median survival of 12.8 years. This finding is consistent with other reports that suggest that improved survival is associated with complete cytoreduction.[15–18] The cause-effect role of surgical cytoreduction, however, is not clear. In this study,

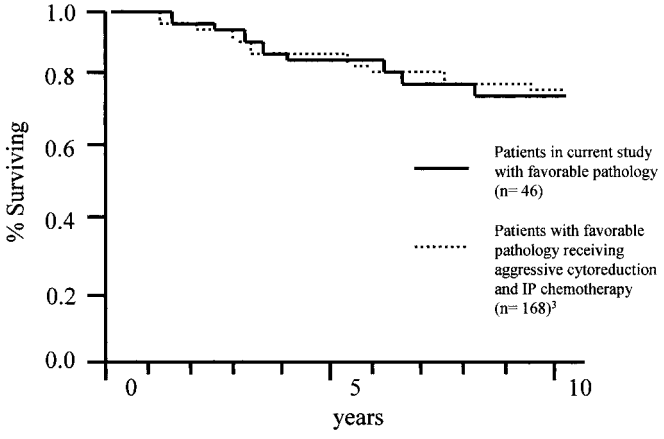


FIGURE 6. Comparison of long-term survival in patients with PMP from studies representing different treatment philosophies. The dotted line represents the overall survival of patients receiving aggressive surgical cytoreduction and intraperitoneal chemotherapy.[3] To be selected for this therapy, patients, by definition, had favorable pathologic characteristics. The black line represents patients from the current study that had comparable favorable pathologic features. The curves were adjusted to reflect similar 10-year time intervals (years on the *x* axis).

more extensive ESS-3 operations were not clearly associated with either improved survival or a greater likelihood of complete cytoreduction. Although it is impossible to directly compare the magnitude of surgical procedures performed between this and other studies, the extent of surgery, as demonstrated by the ESS score, reflects a surgeon-dependent phenomenon that is not independently associated with improved survival in this series. Although pathologic designation was not associated with the ability to achieve complete cytoreduction, the completeness of cytoreduction may reflect a disease-phenomenon (extent of disease) and emerges as more predictive of outcome. It is impossible to say in a retrospective analysis whether it was the impact of treatment (complete cytoreduction), tumor biology, or patient selection that led to the associated survival benefit. Confounding variables such as the timing of intervention (increasing lead time bias in those patients who underwent earlier cytoreduction of low-volume disease) are also impossible to account for in this type of study.

Analysis of recurrence data from this series underscores the limitations of using overall survival as the principal end point in evaluating patients with PMP. Following complete cytoreduction, 91% of the patients in this series experienced disease recurrence, with a median disease-free interval of only 24 months. The disease-free interval was not associated with pathologic subgroup, the extent of surgery, or operation number. Even in patients who experienced the best outcomes, disease recurrence was common. Ninety percent of the 10-year survivors required multiple operation for PMP recurrence, and 77% had evidence of disease either at death or at the completion of follow-up. Other authors have noted that recurrence is common following an operation for PMP. In the Mayo series, 67% of patients ultimately developed recurrence and 50% of recurrence occurred within 2.5 years.[15] Although the short-term recurrence of PMP following aggressive debulking operations has been stated to be in the 35% to 40% range, recurrence data on long-term survivors are unknown from the literature.[1,18] Such incomplete reporting limits the ability to make useful comparisons to the data in this report. These data, however, suggest that a disease-free state is not an absolute requirement for long-term survival in PMP.

Although a demonstrable long-term survival makes it tempting to claim that surgery for PMP is potentially curative, the high likelihood of recurrent disease associated with long-term survival strongly suggests that such claims are imprecise. Although cure, defined as long-term survival free of recurrence, is rare, careful application of surgical interventions may benefit carefully selected patients. Unfortunately, surgical therapy is often viewed in an overly simplistic manner based on either "curative" or "noncurative" designations. In the curative setting, this binary thinking can lead to the application of an overly aggressive approach, with its associated toxicities, until a patient becomes clearly unsalvageable. When "cure" is not possible, it can lead to a therapeutic nihilism that potentially overlooks the importance of sound palliative care. Use of the term *remission*, frequently used to describe stable disease in patients with hematologic malignancies, would be a more accurate way to describe the course of patients with PMP in a disease-free or symptom-free state.[19]

The significance of such terminology is not simply a matter of semantics. During the curative phase of therapy, consequences of treatment such as severe acute toxicity, patient discomfort, and even mortality may be viewed as acceptable risks to achieve prolongation of life.[20] The functional and quality-of-life issues associated with the significant upper and lower GI resections sometimes performed during aggressive surgical procedures for PMP cannot be understated. By predicating decisions with expectations of cure, the surgeon may be encouraging the patient to accept risks that he or she might not otherwise find acceptable. In addition, the presentation of survival data out of context to the natural history of PMP or without relevant recurrence data can potentially "frame" or bias patient decisions in an inappropriate manner. As Lustig and Scardino[21] wrote, "the ethical requirement to avoid framing is especially germane to chronic or slowly progressive conditions, where the data regarding the relative efficacy of treatment alternatives remain unclear, and the tendency to be unwarrantedly enthusiastic regarding one's own specialty and unduly pessimistic about other alternatives must be strongly resisted." Despite an individual patient's enthusiasm regarding such therapy, in such circumstances, the surgeon must show particular caution to avoid minimizing the risks of morbidity and reduced quality of life that might result. By understating the known uncertainties regarding PMP, surgeons not only undermine the informed consent process but also jeopardize the foundations of a strong and enduring therapeutic alliance that will surely be required for the optimal care of the patient during the long-term survival associated with this disease.[22]

Like most other reports on PMP, patient selection plays a major role in any therapy that is used. In this series, the surgical intent of each subsequent operation evolved through the course of the disease. During the initial procedures, operations tended to be more aggressive and more often resulted in complete cytoreduction. Although patients usually had symptoms, asymptomatic patients were brought to operation more frequently for disease only appreciated on radiographic studies or physical examination. This report demonstrates several factors that may explain, in part, surgeons' changing approach to patients with PMP. Following an ESS-3 procedure, subsequent attempts at complete cytoreduction were rarely successful. Perhaps surgeons chose not to offer patients further radical surgery, having already failed at an earlier attempt. Following an earlier operation associated with a major complication, furthermore, patients infrequently

received an additional operation, suggesting that surgeons choose not to select patients for additional procedures following serious morbidity in the past. After initial attempts at more aggressive therapy, operations became progressively more palliative in nature. It is impossible in a report such as this to determine which factors were used by surgeons to select PMP patients for palliative operations. To the authors, it appeared that symptom severity, physical and functional status, expected durability of the procedure, and expected survival of the patient play significant roles in this decision-making process.

PMP remains a disease that follows "an unremitting but prolonged clinical course."[15] Despite a much-improved understanding about the biology of this condition, the impact of therapy is still incompletely understood. Even though complete cytoreduction is associated with prolonged overall survival, recurrence of disease is common and multiple operations are frequently required. Patients may enjoy sustained periods of remission, free of symptoms, but long-term disease-free survival is distinctly uncommon. In attempts to create theoretically attractive and uniform treatment protocols, the critical role of patient selection should not be minimized but rather explored to understand key factors involved in good clinical decision making. One should not forget the wisdom previously expressed by Cady,[23] particularly applicable to the study of PMP. He writes, "in the world of surgical oncology: Biology is king; selection is Queen, and the technical details of surgical procedures are the Princes and Princesses of the realm. Occasionally the prince and princess tries to usurp the throne; they almost always fail to overcome the powerful forces of the King and Queen." In the future, randomized trials utilizing relevant clinical endpoints and appropriate control groups could provide the basis for a better understanding of the role of surgery in PMP. Although many have concluded that the rarity of this disease prevents such a trial, the size of reports now documented in the literature suggest that such efforts in a multicenter setting might be possible.

REFERENCES

1. Hinson FL, Ambrose NS. Pseudomyxoma peritonei. *Br J Surg*. 1998;85: 1332–1339.
2. Sugarbaker PH. Cytoreductive surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. *Eur J Surg Oncol*. 2001;27:239–243.
3. Esquivel J, Sugarbaker PH. Clinical presentation of the pseudomyxoma peritonei syndrome. *Br J Surg*. 2000;87:1414–1418.
4. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis: a clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". *Am J Surg Pathol*. 1995;19:1390–1408.
5. Miner TJ, Jaques DP, Paty P, et al. Symptom control of locally recurrent rectal cancer. *Ann Surg Oncol*. 2002;10:72–79.
6. Miner TJ, Jaques DP, Shriver CD. A prospective evaluation of patients undergoing surgery for the palliation of an advanced malignancy. *Ann Surg Oncol*. 2002;9:696–703.
7. Portilla AG, Sugarbaker PH, Chang D. Second-look surgery after cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer: analysis of prognostic features. *World J Surg*. 1999;23:23–29.
8. American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J Clin Oncol*. 1996;14:671–679.
9. Tamburini M, Casali PG, Miccinesi G. Outcome assessment in cancer management. *Surg Clin North Am*. 2000;80:1–14.
10. Spertus J. Selecting end points in clinical trials: what evidence do we really need to evaluate a new treatment? *Am Heart J*. 2001;142:1–4.
11. Wirtzfeld DA, Rodriguez-Bigas M, Weber T, et al. Disseminated peritoneal adenomucinosis: a critical review. *Ann Surg Oncol*. 1999;6:797–801.
12. Prayson RA, Hart WR, Petras RE. Pseudomyxoma peritonei. A clinicopathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumors. *Am J Surg Pathol*. 1994;18:591–603.
13. Ronnett BM, Yan H, Kurman RJ, et al. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. *Cancer*. 2001;92:85–91.
14. Sugarbaker PH. Pseudomyxoma peritonei: a cancer whose biology is characterized by a redistribution phenomenon. *Ann Surg*. 1994;219: 109–111.
15. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei: long-term patient survival with an aggressive regional approach. *Ann Surg*. 1994;219:112–119.
16. Smith JW, Kemeny N, Caldwell C, et al. Pseudomyxoma peritonei of appendiceal origin: the Memorial Sloan-Kettering Cancer Center experience. *Cancer*. 1992;70:396–401.
17. Wertheim I, Fleischhacker D, McLachlin CM, et al. Pseudomyxoma peritonei: a review of 23 cases. *Obstet Gynecol*. 1994;84:17–19.
18. Sugarbaker PH, Ronnett BM, Archer A, et al. Pseudomyxoma peritonei syndrome. *Adv Surg*. 1996;30:233–280.
19. Wear S, Milch R, Weaver WL. *Care of Dying Patients: Surgical Ethics*. New York: Oxford University Press, NY; 1998:171–197.
20. Miner TJ, Jaques DP, Tavaf-Motamen H, et al. Decision making on surgical palliation based on patient outcome data. *Am J Surg*. 1999;177: 150–154.
21. Lustig A, Scardino P. *Elective Patients: Surgical Ethics*. New York: Oxford University Press; 1998:133–151.
22. McCullough LB, Jones JW, Brody BA. *Informed Consent: Autonomous Decision Making of the Surgical Patient: Surgical Ethics*. New York: Oxford University Press; 1998:15–37.
23. Cady B. Presidential address: basic principles in surgical oncology. *Arch Surg.* 997;132:338–346.