# Pseudomyxoma Peritonei

## *Biological Features Are the Dominant Prognostic Determinants After Complete Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy*

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**Objective:** To investigate outcome and prognostic factors in patients with pesudomyxoma peritonei (PMP) treated by complete cytoreduction and hyperthermic intraperitoneal chemotherapy.

**Background:** After comprehensive treatment, prognosis of PMP is predominantly dependent on the completeness of cytoreduction. Once complete cytoreduction is achieved, additional factors predicting long-term outcome are still poorly understood.

**Methods:** From a prospective database, we selected 102 patients undergoing complete cytoreduction (residual tumor nodules ≤2.5 mm) and closed-abdomen hyperthermic intraperitoneal chemotherapy with mitomycin-C and cisplatin. Previously, 22 patients had systemic chemotherapy. PMP was histologically classified into disseminated peritoneal adenomucinosis, peritoneal mucinous carcinomatosis (PMCA), and intermediate/discordant group. Twenty-one patient-, tumor-, and treatment-related variables were assessed by multivariate analysis with respect to overall (OS) and progression-free (PFS) survival. The following immunohistochemical markers were tested: cytokeratin (CK)-7, CK-20, CDX-2, MUC-2, and MUC-5AC.

**Results:** Operative mortality was 1%. Seventy-eight patients were diagnosed with disseminated peritoneal adenomucinosis, 24 with PMCA, none with intermediate/discordant group. For the overall series, median follow-up, 5-year OS, and PFS were 45 months (range 1–110), 84.4%, and 48.3%, respectively. In most cases, CK20, CDX-2, and MUC-2 were diffusely positive, whereas CK-7 and MUC-5AC were variably expressed. At multivariate analysis, previous systemic chemotherapy and PMCA correlated to both worse OS and PFS, elevated serum CA125 only to worse PFS. CK20, CDX-2, and MUC-2 expression correlated to prognosis at univariate analysis.

**Conclusions:** After complete cytoreduction and hyperthermic intraperitoneal chemotherapy, prognosis of PMP is primarily dependent on pathologic and biologic features. MUC-2, CK-20, and CDX-2 may be related to the disease biology. Understanding PMP molecular basis may facilitate personalized treatment.

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Historically, the term pseudomyxoma peritonei (PMP) refers to a rare condition characterized by mucinous tumor implants throughout the peritoneum and progressive accumulation of mucinous ascites.[1–2] Recent pathologic, molecular, and immunohistochemical studies have provided the evidence that most cases of PMP originate from ruptured low-grade appendiceal mucinous neoplasms.[3–5] Origin from different sites have been exceptionally reported, including stomach,[6] colon,[6] pancreas,[7] urachus,[8] breast,[9] and mucinous ovarian tumor,[10] the latter likely being the most common in this unusual group.

PMP has been conventionally treated by serial debulking and palliative intraperitoneal or systemic chemotherapy. Because of the rarity of the disease, limited results from historical case series are available. These reports suggest that at best long-term survival of 20% to 30% can be achieved, as conventional treatments usually result in multiple disease recurrences and patients ultimately die of intra-abdominal progression.[11–14] In recent years, improved survival has been associated to a new local-regional comprehensive approach.[15–19] This treatment strategy combines macroscopic surgical cytoreduction by means of peritonectomies and multivisceral resections with microscopic chemical cytoreduction by means of perioperative-heated intraperitoneal chemotherapy.

Other groups and our group[15–19] have repeatedly demonstrated that the completeness of the surgical cytoreduction is the dominant prognostic feature in patients with PMP, presumably because of the limited penetration of local-regional chemotherapy into residual peritoneal tumor.[20] Despite the accomplishment of optimal cytoreduction, recurrences are not uncommon and still represent a substantial cause of mortality for these patients.[18–19] To date, however, additional risk factors for poor long-term prognosis have never been thoroughly investigated in the subset of patients undergoing optimal cytoreduction. Paradoxically, patients undergoing grossly incomplete cytoreduction have been more extensively assessed.[21] Additionally, basic science investigations of PMP have been undertaken only in recent years[22–26] and reliable biologic or molecular prognostic determinants are still lacking.

The objective of the present study was to analyze a prospective database to address survival results and potential prognostic variables in patients affected by mucinous appendiceal neoplasm with peritoneal dissemination treated by cytoreduction with no visible or millimetric residual disease, combined with hyperthermic intraperitoneal chemotherapy (HIPEC). These eligibility requirements were designed to assess the impact of clinicopathologic variables on outcome after optimal combined treatment. Furthermore, biologic markers related to the origin and peculiar clinical features of PMP were investigated with a special focus on their correlation to survival.

## PATIENTS AND METHODS

All the patients included in the present study were treated according to a protocol approved by the Institutional Ethics Committee and signed a written informed consent form. Data for the present analysis were derived from the prospective database of patients undergoing cytoreduction and HIPEC at the National Cancer Institute (Milan, Italy). Additional information was collected from the medical charts.

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## Patient Selection

Eligibility criteria for combined treatment included: histologic diagnosis of PMP made or confirmed in our Pathology Department; age ≤75; performance status ≤2 according to the Eastern Cooperative Oncology Group (ECOG) score[27]; no significant comorbidities; no extraperitoneal metastases; and peritoneal disease amenable to potentially complete cytoreduction at preoperative computed tomography (CT)-scan.[28]

Additional inclusion criteria for the present study consisted of mucinous appendiceal neoplasm with peritoneal dissemination undergoing complete cytoreduction and HIPEC. Appendiceal origin was documented on pathologic examination (n = 49) or slide review (n = 24). Cases without slides of the appendix available for review were deemed to have an appendiceal origin if there was a clinical history of an appendiceal neoplasm and no normal appendix or colorectal primary carcinoma were identified (n = 29). Peritoneal dissemination was defined on the basis of intraoperative findings as localized or diffuse accumulation of mucinous tumors in the peritoneal cavity. Tumors with >50% extracellular mucin were defined as mucinous. The completeness of cytoreduction (CC) was classified at the end of the surgical phase according to Sugarbaker criteria—CC-0: no macroscopic residual disease; CC-1: residual disease ≤2.5 mm in any region; CC-2: residual disease >2.5 mm and ≤25 mm; and CC-3: residual disease >25 mm.[29] CC-0/1 cytoreduction was considered complete. This inclusion criterion was based on the hypothesis that tumors of ≤2.5 mm can be potentially penetrated by intraperitoneal chemotherapy.[20]

From June 1996 to May 2008, 127 consecutive patients with PMP were operated on by the same surgical team with the aim of performing complete cytoreduction and HIPEC. The following patients were excluded: suboptimal (CC-2/3) cytoreduction (n = 7), debulking/palliative surgery (n = 11), nonappendiceal origin (colon: n = 1; intestinal-type mucinous ovarian tumor associated with mature cystic teratoma: n = 2; unknown: n = 2), adenocarcinoid (n = 1), and intestinal-type (n = 1) histology. Eventually, 102 patients were selected for the present analysis. Clinical characteristics of the entire case series are shown in Table 1. Some of these patients were reported previously.[6,19]

Before referral, 22 patients underwent a median of 6 cycles of systemic chemotherapy (mean 7.2; range 4–15) and 2 had radiotherapy. Limited information are available, as these treatments were not given at our institution, but no major response was observed.

**TABLE 1.** Clinicopathological Characteristics of 102 Patients With Pseudomyxoma Peritonei

| Variable | N |
|---|---|
| Gender M/F | 44/58 |
| Age (yr), median (range) | 53.5 (24–76) |
| ECOG | 74 |
| Category 0 | 74 |
| Category 1 | 25 |
| Category 2 | 3 |
| Previous systemic chemotherapy | |
| Not done | 80 |
| Done | 22 |
| FOLFOX | 6 |
| FOLFIRI | 4 |
| 5-FU/folinic acid | 4 |
| Carboplatin + paclitaxel | 3 |
| Oxaliplatin + gemcitabine | 2 |
| Cisplatin containing | 4 |
| Other | 2 |
| Previous surgical procedures | |
| Only biopsy | 27 |
| 1 region dissected | 21 |
| 2–5 regions dissected | 49 |
| >5 regions dissected | 5 |
| Histology | |
| DPAM | 78 |
| PMCA | 24 |
| PCI, mean (range) | 21.8 (3–39) |
| Interval diagnosis/HIPEC (mo), median (range) | 5 (2–53) |
| Preoperative serum CEA >5 ng/mL | 63* |
| Preoperative serum CA19.9 >37 U/mL | 53* |
| Preoperative serum CA125 >35 U/L | 44† |

*Data missing in 3 patients.
†Data missing in 18 patients.
PCI indicates peritoneal cancer index.

## Operative Treatment

The details of the operative technique adopted in our center have been described previously.[19] Briefly, the goal of the surgical cytoreduction was to remove all the visible tumor by the following procedures: (1) right subdiaphragmatic and parietal peritonectomy, (2) left subdiaphragmatic and parietal peritonectomy, (3) greater omentectomy with splenectomy, (4) lesser omentectomy and stripping of the omental bursa, and (5) pelvic peritonectomy with salpingo-oophorectomy in women. Depending on disease extent, implants on visceral surfaces were removed by electrosurgical local dissection or multivisceral resections including Glisson capsule dissection, cholecystectomy, partial or total gastrectomy, sigmoid, and right or total colectomy.

HIPEC was performed according to the closed-abdomen technique for 60 minutes, at a temperature of 42.5°C, with cisplatin (25 mL/m$^2$/Lt of perfusate) plus mitomycin-C (3.3 mg/m$^2$/Lt of perfusate). Perfusate volume was 4 to 6 Lt, and average flow 700 mL/min. The extracorporeal circulation device Performer LRT (RAND, Medolla, Italy) was used.

The peritoneal cancer index was used at surgical exploration to score the extent of peritoneal involvement.[30] The extent of previous surgery was categorized according to the number of abdominopelvic regions dissected.[15] According to Ronnett, PMP was histologically classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and intermediate or discordant feature group (ID).[3]

Representative paraffin blocks of peritoneal lesions were selected, and the following immunohistochemical studies were performed using the avidin-biotin complex immunoperoxidase technique: MUC-2, MUC-5AC, CDX-2, cytokeratin (CK)-7, and CK-20. The details of the studies mentioned above were reported previously.[6] The immunohistochemistry stains were scored according to the number of positive cells as: 0 = none; 1 ≤ 25%; 2 = 26% to 50%; 3 = 51% to 75%; and 4 = 76% to 100%. The staining intensity was scored as: 0 = no staining; 1 = weak; 2 = moderate; 3 = strong, resulting in a range of 0 to 7. A value ≤2 was considered negative, a value equal to 3 was considered weak, and a value >3 was considered positive.

No patients were lost to postoperative follow-up. Physical examination, thoracic/abdominal CT scan, and serum marker measurements (CEA, CA19.9, CA125) were performed every 3 months during the first 2 years and every 6 months afterward. Postoperative disease progression was confirmed at surgical exploration or by

CT-scan/ultrasound-guided biopsy. Alternatively, it was defined according to the Response Evaluation Criteria in Solid Tumor Group.[31]

## Statistics

The study end-point were overall survival (OS) and progression-free survival (PFS). Survival rates were calculated according to the Kaplan-Meier method.[32] OS as from the day of cytoreduction with HIPEC to the time of death because of any cause; PFS was dated from the day of cytoreduction with HIPEC to the time of postoperative disease progression. Patients with uneventful postoperative course were censored at the time of last follow-up visit. The following independent variables, chosen on the basis of literature information, were assessed: age, sex, histologic variant, ECOG performance status, preoperative systemic chemotherapy, extent of previous surgery, interval between diagnosis and combined treatment, peritoneal cancer index, number of cytoreductive surgical procedures, cisplatin and mitomycin-C total dosage, preoperative serum marker determinations, and immunohistochemical studies. The 2-tailed log-rank test was used to assess the significance of the comparison between survival distributions. Multivariate analysis of factors deemed statistically significant by univariate analysis was performed by the Cox proportional hazard model.[33] The backward elimination method was used to determine which clinical variables best correlated to survival. All statistical analyses were conducted by SPSS software version 8.0.0 for Windows (SPSS Inc., Chicago, IL). $P$ value $<0.05$ was considered significant.

# RESULTS

The details of the 102 combined procedures are summarized in Table 2. Cytoreduction was rated as CC-0 in 35 patients and as CC-1 in 67. Median follow-up was 45 months (range 1–131) for the entire series. Operative mortality occurred in 1 patient who died on the 21st postoperative day from duodenal perforation and abdominal hemorrhage.

During the study period, disease progression occurred in 32 patients, involving the abdomen in 21 cases, the pleural cavity in 5, and both in 6. At the time of the present analysis, 75 patients were disease free (including 5 patients who were treated for progressive disease) 16 were alive with disease, 8 died for the disease, and 3 died for causes not related to the disease. Five- and 10-year OS was 84.4% and 79.4%, respectively; 5- and 10-year PFS was 48.3%. OS and PFS curves are shown in Figure 1.

## Prognostic Factors

Seventy-eight patients were histologically diagnosed with DPAM, 24 with PMCA, and none with intermediate or discordant feature group. CC-0 cytoreduction was accomplished in 9 patients with PMCA and in 26 with DPAM, whereas CC-1 cytoreduction was achieved in 15 patients with PMCA and in 52 with DPAM; the difference was not significant ($\chi^2 = 0.848$). The appendix was available for pathologic evaluation in 71 patients. Primary lesions were diagnosed as low-grade appendiceal mucinous neoplasm in 62 cases and mucinous adenocarcinoma in 9.[13]

The results of the immunohistochemical studies are summarized in Figure 2. Because of the sparse epithelial and the high mucin component of PMP, immunohistochemistry results were available only for 85 patients. Strong expression of CDX-2 in a uniform nuclear staining pattern and of CK20 in a uniform cytoplasmic pattern was seen in nearly all peritoneal tumors; conversely, CK7 mostly showed heterogeneous and weak immunoreactivity. In nearly all tumors, MUC-2 was strongly and diffusely positive, whereas MUC-5AC was variably expressed. No correlation between marker expression and histologic subtypes was seen (data not shown).

**TABLE 2.** Cytoreductive Surgery and HIPEC Data for 102 Combined Procedures

| Procedures | N |
|---|---|
| Peritonectomies | |
| Right upper quadrant | 99 |
| Left upper quadrant | 100 |
| Pelvic | 101 |
| Greater omentectomy | 99 |
| Lesser omentectomy | 99 |
| Mean | 4.88 |
| Median (range) | 5 (3–5) |
| Multivisceral resections | |
| Glisson's capsule resection | 65 |
| Cholecistectomy | 65 |
| Partial/total gastrectomy | 10/17 |
| Splenectomy | 87 |
| Right colectomy | 53 |
| Appendectomy | 18 |
| Sigmoidectomy | 49 |
| Total colectomy | 7 |
| Small bowel resection | 24 |
| TAH-BSO | 15 |
| Other | 21 |
| Mean | 4.22 |
| Median (range) | 4 (1–8) |
| Completeness of cytoreduction | |
| No visible residual tumour | 35 |
| Residual tumour ≤2.5 mm | 67 |
| Mitomycin-C dose | |
| Mean, mg | 29.2 |
| Median (range) | 30 (15–50) |
| Cisplatin dose | |
| Mean, mg | 201.2 |
| Median (range) | 200 (100–300) |

TAH indicates total abdominal histerectomy; BSO, bilateral salpingo-oophorectomy.

At univariate analysis, CK-20 expression correlated to both overall and progression-free survival, whereas MUC-2 and CDX-2 expression correlated only to OS. Median OS was 14 months (range 4–48) for patients with negative/weak CK-20, 47 months (range) for those with negative/weak MUC-2 (range 14–72), and 32 months (range 7–47)) for those with negative/weak CDX-2. Median OS was not reached in patients with positive CK-20 ($P = 0.0007$), MUC-2 ($P = 0.0251$), and CDX-2 ($P = 0.0057$). Median PFS was 6 months (range 5–23) in patients with positive CK-20 and not reached in those with negative/weak marker ($P < 0.0001$). Further analyses were performed to determine if a combination of staining characteristics is predictive of outcome. At univariate analysis, OS was statistical better for patients with positive CK-20, CDX-2, and MUC2, as compared with those with at least one negative/weak marker ($P = 0.0110$).

Univariate and multivariate analysis of potential patient-, tumor-, and treatment-related prognostic factors is shown in Table 3. Six variables (PMCA histologic variant, preoperative systemic chemotherapy, negative/weak CK-20, CDX-2, and MUC-2 and at least 1 negative/weak marker) univariately correlated to decreased OS. Seven variables correlated to decreased PFS (PMCA histologic variant, preoperative systemic chemotherapy, ECOG score = 1–2,

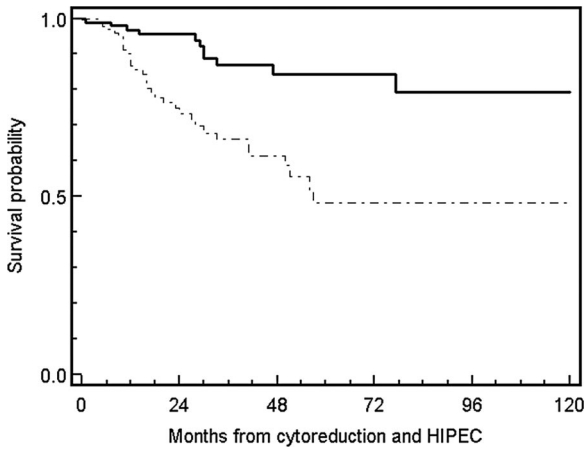


**FIGURE 1.** Overall (darker line) and progression-free survival (lighter line) in 102 patients with pseudomyxoma peritonei treated by complete cytoreduction and HIPEC.

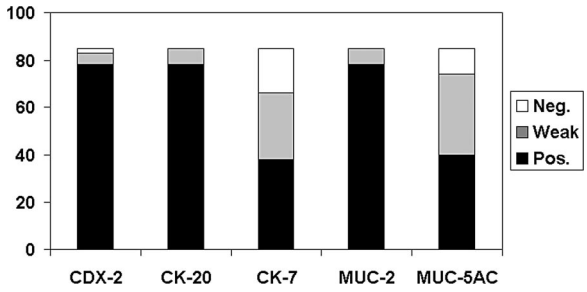


**FIGURE 2.** Immunohistochemical results in 85 patients with pseudomyxoma peritonei.

interval between diagnosis and HIPEC >6 months baseline serum CA125 >35 U/L, CEA >5 ng/mL, negative/weak CK-20). After multivariate analysis, PMCA histologic variant, and preoperative systemic chemotherapy retained prognostic significance for both reduced OS and PFS; increased CA125 was recognized as an independent predictor of reduced PFS.

## DISCUSSION

Because of its unique clinicopathological features, with the predictable pattern of peritoneal dissemination and virtually no systemic involvement, pseudomyxoma peritonei is considered a paradigm for the management of peritoneal malignancies of any other origin.[1–2] Improved survival after surgical cytoreduction and local-regional perioperative chemotherapy has been reported, resulting in an increasing interest in using comprehensive strategies to treat carcinomatosis from gastrointestinal or gynaecological cancers.[15–19] A common feature of these studies is that outcome is predominantly determined by the completeness of the cytoreduction. Patients with PMP who are able to undergo complete cytoreduction may expect long-term survival and even definitive cure.

Although no formal literature statement is available, inherent biologic tumor characteristics presumably predispose some patients to complete cytoreduction and hence to prolonged survival. Accordingly, these patients should represent a relatively uniform and favorable subset. Their biologic behavior, however, is highly variable and some of them succumb to rapidly progressive recurrent disease.[16–19] Clearly, the completeness of cytoreduction is often insufficiently discriminatory, but additional factors predicting prognosis after adequate cytoreduction have not been extensively addressed.

Limited literature data on patients with PMP undergoing optimal combined treatment are available. Prognostic factors have been assessed by multivariate analysis in relatively large series (Table 4). However, because these studies included 10.3% to 36.4% of patients with incomplete cytoreduction, as well as extra-appendicular or nonmucinous primary tumors, extrapolation of results is questionable. To our knowledge, only 2 studies specifically addressed the outcome of patients who had complete cytoreduction. In a series of 402 patients, disease recurrence was the only independent risk factor for reduced OS, but the study was actually designed to assess the pattern of failure.[34] In a smaller French study, pathologic grading univariately correlated to survival.[35] The experience of the Washington Cancer Centre is the most representative, but increasingly aggressive local-regional chemotherapy regimens were used over the years.[15,16,34] Conversely, the present study included only cases of PMP originating from mucinous appendiceal malignancies treated by the same standardized protocol with minimal treatment-related bias.

The combination of cytoreductive surgery and HIPEC is expensive, time consuming, and related to high rates of potential life-threatening morbidity.[15–19] A more accurate prognostic assessment would be needed to design individualized multimodality treatment plans and to define the appropriate level of surgical and comprehensive aggressiveness for the individual patients. Reliable prognostic indicators may have practical implications in the standardization of supplementary therapeutic options for high-risk patients, such as second-look surgery,[36] early postoperative intraperitoneal chemotherapy,[15] and adjuvant systemic or targeted therapy.[25]

The clinical entity pseudomyxoma peritonei comprises a wide morphologic and biologic spectrum of aggressiveness. Controversies still surround its pathologic classification; particularly, there is no agreement as to the point of separation between histologically bland, "benign" lesions and mucinous adenocarcinoma. Ronnett categorized PMP into adenomucinosis and mucinous carcinomatosis, with an intermediate group.[3] The author suggested that only adenomucinosis associated with appendiceal cystadenoma should be referred to as PMP. Recently, based on the clinically malignant behavior of all-type PMP, Bradley et al have proposed that mucinous carcinoma peritonei, either low grade or high grade, is best applied to all cases of PMP.[37] We tentatively applied Ronnett 3-tiered classification, but we failed to assign cases to the intermediate group. Consequently, a fundamentally binary classification was used retrospectively in the first 39 cases and prospectively afterward.[6]

At multivariate analysis, systemic chemotherapy administered before referral to our center correlated to worse OS and PFS. Systemic chemotherapy has been assessed by our and other groups[16–17] but only in a previous study including also patients undergoing grossly incomplete or palliative surgery it correlated to survival.[19] We hypothesized that tumor biology may have played a role in this setting, because it is reasonable that only patients with seemingly aggressive disease received systemic treatment. Our findings raises concern as to the possible role of prior chemotherapy in selecting more aggressive tumor cell clones. This relevant issue could be addressed by biologic investigations.

A set of biologic markers related to PMP origin and clinical features was investigated. Their value in differentiating mucinous disseminations of appendiceal versus not-appendiceal origin was discussed previously.[6,19] In the present article, we focused on their potential prognostic significance by reviewing a larger number of cases with longer follow-up. At univariate analysis, reduced OS correlated to negative/weak CK-20, CDX-2, and MUC-2. These

**TABLE 3.** Univariate and Multivariate Analysis of Prognostic Factors in 102 Patients Undergoing Complete Cytoreduction and HIPEC

| | Overall Survival | | | Progression-Free Survival | | |
|---|---|---|---|---|---|---|
| | Univariate | Multivariate | | Univariate | Multivariate | |
| | *P* | RR (95% CI) | *P* | *P* | RR (95% CI) | *P* |
| Sex (male vs. female) | 0.372 | | | 0.737 | | |
| Age (>53.5 vs. ≤53.5) | 0.940 | | | 0.085 | | |
| ECOG (1–2 vs. 0) | 0.249 | | | 0.005 | 1.83 (0.97–3.44) | 0.060 |
| Months from diagnosis (>6 vs. ≤6) | 0.169 | | | 0.045 | 0.97 (0.42–2.24) | 0.950 |
| Systemic CT (done vs. not done) | 0.002 | 5.04 (1.51–16.91) | 0.009 | <0.001 | 3.14 (1.40–7.04) | 0.005 |
| Extent of previous surgery (>1 vs. ≤1 abdominal region dissected) | 0.134 | | | 0.497 | | |
| PCI (>12 vs. ≤12) | 0.151 | | | 0.210 | | |
| Histology (PMCA vs. DPAM) | 0.004 | 4.69 (1.40–15.69) | 0.012 | <0.001 | 3.69 (1.67–8.18) | 0.001 |
| Completeness of cytoreduction (CC-0 vs. CC-1) | 0.687 | | | 0.329 | | |
| CEA (>5 ng/mL vs. ≤5 ng/mL)* | 0.134 | | | 0.010 | 2.26 (0.83–6.166) | 0.109 |
| Ca19.9 (>37 U/mL vs. ≤37 U/mL)* | 0.685 | | | 0.072 | | |
| Ca125 (>35 U/L vs. ≤35 U/L)† | 0.360 | | | 0.001 | 3.09 (1.06–9.01) | 0.039 |
| MUC-2 (neg/weak vs. pos)‡ | 0.025 | 1.70 (0.04–65.79) | 0.775 | 0.506 | | |
| MUC-5AC (neg/weak vs. pos)‡ | 0.591 | | | 0.516 | | |
| CK-20 (neg/weak vs. pos)‡ | 0.001 | 0.39 (0.01–10.23) | 0.571 | <0.001 | 1.16 (0.38–3.57) | 0.796 |
| CK-7 (neg/weak vs. pos)‡ | 0.873 | | | 0.875 | | |
| CDX-2 (neg/weak vs. pos)‡ | 0.006 | 0.51 (0.05–5.03) | 0.567 | 0.273 | | |
| MUC-2/CK-20/CDX-2 (≥1 neg/weak marker vs. 3 pos markers) | 0.011 | 1.12 (0.02–59.39) | 0.953 | 0.126 | | |
| Cytoreductive procedures (>4 vs. ≤4) | 0.142 | | | 0.341 | | |
| Mitomycin-C dose (≤30 mg vs. >30 mg) | 0.652 | | | 0.569 | | |
| Cisplatin dose (≤200 mg vs. >200 mg) | 0.139 | | | 0.242 | | |

*Data missing in 3 patients.
†Data missing in 18 patients.
‡Data missing in 17 patients.
CC-0, no visible residual tumour; CC-1, residual tumour ≤2.5 mm; CT, chemotherapy.

**TABLE 4.** Comparison of Prognostic Multivariate Analyses in Series of >100 Patients With Pseudomyxoma Peritonei Treated by Cytoreduction and HIPEC

| Centre | Pts. (n.) | Append. npl (%) | Nonmucinous npl (%) | Complete SCR (%) | Median Follow-Up (Mo) | Prognostic Factors |
|---|---|---|---|---|---|---|
| Washington[15] | 385 | NS | — | 64.9 | 37.6 | OS: CC, pathology; PSS |
| Washington[16] | 501 | 100 | 1.1 | NS | 48 | OS: 2° neoplasm; CC, pathology |
| Wake Forest[17] | 110 | 100 | 7.2 | 63.6 | 34.8 | OS: age, performance status; HIPEC duration, CC; interval diagnosis/HIPEC |
| Amsterdam[18] | 103 | 89.3 | — | 89.7 | 51.5 | OS: sex, pathology; PFS: CC, sex, pathology |
| Milan[19] | 104 | 95.2 | — | 85.6 | 37 | OS: CC, previous syst. CT, pathology; PFS: CC, previous syst. CT, pathology, baseline CA19.9 |
| Present series | 102 | 100 | — | 100 | 45 | OS: previous systemic CT, pathology; PFS: previous systemic CT, pathology, baseline CA125 |

NS indicates not stated; SCR, surgical cytoreduction; PSS, prior surgical score; CC: completeness of cytoreduction; CT, chemotherapy.

observations, though novel, are not surprising given the current information on these markers in other malignancies. CDX-2 is a member of the caudal-related homeobox gene family, which plays a crucial role in cell proliferation and differentiation[38]; its status in PMP has been investigated by our group.[6] Weak CDX-2 expression has been associated to poor prognosis in gastric, biliary, and colon cancer.[39] Analogously, cytokeratins are involved in cellular differentiation and CK-20 positivity is more frequent in low-grade than in high-grade colorectal carcinoma.[40]

The excess extracellular mucin accumulation is the hallmark of PMP. O'Connell demonstrated that the disease results from MUC-2 over-expression, making it a potential target for translational approaches.[22] Literature data on MUC-2 prognostic significance are controversial, because marker expression seems to be

independent of the degree of malignant transformation.[22] On the other hand, consistently with our findings, MUC-2 was suggested to be a possible tumor suppressor probably related to the disease minimally invasive behavior.[41]

From our data, patients with positive CK-20, CDX-2, and MUC-2 have better OS then those with at least 1 negative marker. It is possible that the lack of significance at multivariate analysis would change with a larger number of cases. Strong expression of these 3 markers is specific with appendiceal origin, whereas MUC-5AC and CK-7 expression is not.[6] Our observations suggest that failure to express the "typical" appendiceal pattern predict aggressive behavior. Interestingly, 4/7 patients with the "atypical" pattern were men, excluding a possible ovarian origin of their disease.

Baseline-increased CA125 independently correlated to reduced progression-free survival. In a previous article, including both adequately and suboptimally cytoreduced patients, baseline CA125 predicted the completeness of cytoreduction.[42] Other groups reported the prognostic value of CEA and CA19.9.[43] Taken together, these data suggest that serum markers reflect tumor aggressiveness and provide accurate prognostic information, but it is presently unclear which set of markers could more reliably predict outcome.

A possible criticism of the present study involves the definition of adequate cytoreduction. The 2.5-mm cut-off between optimal and inadequate residual disease is based on the maximal tumor penetration of intraperitoneal cisplatin,[20] whereas mitomycin-C has probably a lower penetration depth.[44] These values were obtained in mice under experimental conditions, being not necessarily true in the operating room. Different drugs, temperatures, or perfusion techniques may imply different tumor penetration. Analogously to any other series, the measurement of residual disease was made intraoperatively by the surgeon and unobserved incompleteness of cytoreduction may result in treatment failure. Despite such limitations, the completeness of cytoreduction is the most consistent prognostic variable.

The relative contribution of HIPEC to cytoreductive surgery is still poorly known. In the present series, failure to demonstrate a significant survival difference after CC-0 versus CC-1 cytoreduction might support HIPEC effectiveness to eradicate minimal residual disease. Furthermore, no correlation was seen between the completeness of cytoreduction and histologic grading, thus suggesting that factors presumably related to tumor biology, such as resistance or poor permeability to the intraperitoneal chemotherapy, could explain treatment failure.[34] These conclusions, however, should be taken with caution, because of the above mentioned controversies regarding residual disease assessment. Pharmacokinetic studies presently ongoing in our center to determine in vivo drug penetration during closed-abdomen HIPEC might better clarify this issue.

In conclusion, our findings suggest that outcome of PMP after optimal combined treatment is determined by factors directly or indirectly related to tumor biology, such as histologic features, serum or immunohistochemical markers, and responsiveness to systemic treatment. These data, therefore, may contribute to develop individualized comprehensive treatment strategies and support the need of further molecular and cellular investigations.

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