Annals of Surgical Oncology, **13**(5): 624–634
DOI: 10.1245/ASO.2006.03.075

Appendiceal Neoplasms With Peritoneal Dissemination: Outcomes After Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy

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Background: Appendiceal neoplasms frequently present with peritoneal dissemination (PD) and have a clinical course marked by bowel obstruction and subsequent death. Few data have correlated outcome with appendiceal histology after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy (IPHC). We have reviewed our experience with cytoreductive surgery and IPHC for PD from the appendix.

Methods: A total of 110 cases of PD from proven appendiceal neoplasms treated with IPHC were identified from a prospectively managed database. Tumor samples were classified on pathologic review as disseminated peritoneal adenomucinosis (n = 55), peritoneal mucinous carcinomatosis (PMCA) with intermediate features (n = 18), PMCA (n = 29), or high-grade nonmucinous lesions (n = 8). A retrospective review was performed with long-term survival as the primary outcome measure.

Results: A total of 116 IPHCs were performed on 110 patients for appendiceal PD between 1993 and 2004. The 1-, 3-, and 5-year survival rates for all cases were 79.9% ± 4.1%, 59.0% ± 5.7%, and 53.4% ± 6.5%, respectively. When stratified by histology, disseminated peritoneal adenomucinosis and intermediate tumors had better 3-year survival rates (77% ± 7% and 81% ± 10%) than PMCA and high-grade nonmucinous lesions (35% ± 10% and 15% ± 14%; $P = .0032$ for test of differences between groups). Age at presentation ($P = .0134$), performance status ($P < .0001$), time between diagnosis and IPHC ($P = .0011$), resection status ($P = .0044$), and length of hyperthermic chemoperfusion ($P = .0193$) were independently associated with survival.

Conclusions: The data show that long-term survival is anticipated in most patients who are treated with cytoreduction and IPHC for appendiceal PD. The findings presented herein underscore the important prognostic characteristics that predict outcome after IPHC in patients with PD. In all, this work establishes a framework for the consideration of IPHC in future trials for appendiceal PD.

Received March 15, 2005; accepted August 16, 2005; published online March 14, 2006.

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Key Words: Peritoneal dissemination—Disseminated peritoneal adenomucinosis—Peritoneal mucinous carcinomatosis—Intraperitoneal hyperthermic chemotherapy—Mitomycin C—Cytoreductive surgery.

Appendiceal malignancies are rare, with an age-adjusted incidence of approximately .12 cases per 1,000,000 individuals per year.[1] Appendiceal tumors are infrequently diagnosed before surgery and often present with peritoneal dissemination. In cases with low-grade cytology, this peritoneal dissemination is hypothesized to arise from perforation of the appendiceal tumor and subsequent dissemination of mucus-producing adenomatous epithelial cells throughout the abdomen and pelvis. This may lead to mucinous ascites or pseudomyxoma peritonei (PMP). In cases with high-grade cytology, the peritoneal dissemination is usually seen in association with an invasive mucinous carcinoma of the appendix.

The optimal management of patients with peritoneal dissemination of appendiceal neoplasms is a matter of intense debate. Systemic chemotherapy for peritoneal surface spread of appendiceal neoplasms is largely ineffective because of its limited entry into the peritoneum. Furthermore, some tumor cells are resistant to chemotherapy alone. The localization of tumor within the parietal peritoneum without distant metastasis makes an aggressive regional approach attractive. Several groups have treated peritoneal surface extension of appendiceal tumors with debulking procedures.[2–4] However, it is clear that these procedures are frequently unable to remove all microscopic tumor. These patients ultimately experience bowel obstruction and death.

Recent studies, however, have evaluated several alternative treatment modalities for such patients. These procedures have included maximal tumor debulking coupled with adjuvant systemic chemotherapy, normothermic intraperitoneal chemotherapy,[3] photodynamic therapy,[5] and external beam radiotherapy.[3] None of these treatment plans has significantly improved the clinical course in this subset of patients.

One approach to peritoneal dissemination from appendiceal tumors has been optimal cytoreduction surgery (CS) followed by intraperitoneal hyperthermic chemotherapy (IPHC). The cytoreduction always includes a complete omentectomy and an attempt at complete resection, which may entail a multivisceral resection. Selective patients undergo repeat exploration and perfusion as dictated by their performance status and symptoms.[6]

A previous report from our institution suggests that a small number of patients with peritoneal dissemination from appendiceal primary tumors had superior outcomes compared with those with colon, gastric, and pancreatic primary tumors after treatment with CS and IPHC.[7] However, data on prognostic factors for this procedure in the setting of appendiceal primary tumors are limited. We examined a prospective database of patients undergoing CS and IPHC for peritoneal surface malignancy from appendiceal primary tumors to determine the clinicopathologic factors that were independent predictors for overall survival (OS).

METHODS

Patients

Patients who underwent IPHC for peritoneal dissemination from an appendiceal primary tumor at Wake Forest University School of Medicine Baptist Hospital between 1993 and 2004 were identified from a prospective database. All patients evaluated in this study were ≥18 years of age and had normal organ function (serum creatinine <2 mg/dL or creatinine clearance ≥60 mL/min and alkaline phosphatase and serum glutamic-oxaloacetatic transaminase [aspartate transaminase] or serum glutamate pyruvate transaminase [alanine transaminase] <3 times the upper limit of normal), a white blood cell count ≥4,000/μL, and a platelet count ≥100,000/μL. Clinical data on all patients were recorded in a database and maintained by a dedicated data management unit.

Cytoreductive Surgery

Cytoreductive surgery (CS) consisted of the removal of all gross tumor and involved organs, peritoneum, or tissue deemed technically feasible and safe for the patient. Any tumors adherent or invasive to vital structures that could not be removed were cytoreduced by using the cavitational ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO). Peritonectomy procedures were performed as indicated. The resection status of patients was judged after CS by using the following classification: R0,

complete removal of all visible tumor and negative cytological findings or microscopic margins; R1, complete removal of all visible tumor and positive postperfusion cytological findings or microscopic margins; R2a, minimal residual tumor, nodule(s) measuring ≤.5 cm; R2b, gross residual tumor, nodule >.5 cm but ≤2 cm; and R2c, extensive disease remaining, nodules >2 cm.

Intraperitoneal Hyperthermic Chemotherapy

Patients were cooled to a core temperature of approximately 34°C to 35°C by passive measure (i.e., not warming airway gases or intravenous solutions and cooling the room). After CS was completed, peritoneal perfusion inflow and outflow catheters were placed percutaneously into the abdominal cavity. Temperature probes were placed on the inflow and outflow catheter tips. The abdominal skin incision was closed temporarily with a running cutaneous suture to prevent leakage of peritoneal perfusate. A perfusion circuit was established with approximately 3 L of Ringer's lactate. Flow rates of approximately 600 to 800 mL/min were maintained using by a roller pump managed by the pump technician. The circuit continued through a single roller pump and through a heat exchanger and then to the patient.

Constant temperature monitoring was performed at all temperature probes. Once inflow temperature exceeded 38.5°C, 30 mg of mitomycin C (MMC) was added to the perfusate, and at 60 minutes an additional 10 mg of MMC was added to keep MMC perfusate concentrations >5 μg/mL. A maximum inflow temperature of 42.0°C was realized during perfusion, with a target outflow temperature at the pelvis of 40°C. The abdomen was gently massaged throughout perfusion to improve drug distribution to all peritoneal surfaces. The total planned perfusion time after the initial addition of MMC was 120 minutes. In certain patients (elderly individuals, those with extensive previous chemotherapy, those with inanition or poor performance status, and those with extensive peritoneal stripping during surgery), reductions in the dose of MMC (to 30 mg total) or perfusion time (to 60–90 minutes) were made because of concerns about potential toxic effects.

Histological Characterization of Appendiceal Tumors

Tumors gathered from the CS from all patients were evaluated histologically by two pathologists (R.F.B. and K.R.G.). Tumors were categorized as PMP or high-grade nonmucinous tumors. Pseudomyxoma peritonei was further subclassified as disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), or intermediate/hybrid groups according to the work of Ronnett et al.[8] Tumors demonstrating little cytological atypia or mitotic activity, scant simple to focally proliferative cellularity, and abundant extracellular mucin were classified as DPAM. Neoplasms with abundant cellularity associated with architectural and cytological features of carcinoma were classified as PMCA. Tumors with cytological features of both DPAM and PMCA were labeled as PMCA/intermediate. Adenocarcinoma (nonmucinous), adenocarcinoids, and carcinoids of the appendix were labeled as high-grade tumors.

Clinical Follow-Up

Clinical follow-up occurred at 1 and 3 months and then every 3 to 6 months thereafter for up to 1 year. After 1 year, follow-up was at 6-month intervals or less frequently if the patient continued to remain without evidence of disease. Abdominal and pelvic computed tomographic scans were obtained at 3, 6, and 12 months after surgery or when clinically indicated. Some patients received systemic chemotherapy at the discretion of their medical oncologists.

Statistical Analysis

All data were collected prospectively; descriptive statistics were generated for all measures, including means, ranges, and standard deviations for continuous measures and frequencies and proportions for categorical data. OS was calculated from the date of CS and IPHC to the last known date of follow-up or the date of death. Estimates of survival were calculated by using the Kaplan-Meier (product-limit) method; analysis with Cox proportional hazards was performed on all pertinent clinicopathologic variables to determine each one's association with survival. Group comparisons of OS were performed by using the approximate χ^2 statistic for the log-rank test. Additionally, the Cox proportional hazards regression model was used in a stepwise fashion to perform a multivariate analysis of clinicopathologic factors to determine an overall model of independent predictors of OS. Statistical significance was defined as a P value ≤.05.

TABLE 1. *Clinicopathologic data for 110 patients undergoing CS and IPHC for peritoneal surface malignancies from appendiceal neoplasms*

Characteristic	No. of patients	%
Sex		
Male	53	48
Female	57	52
Race		
White	98	89
Black	12	11
Previous treatment		
Debulking procedure	65	59
Chemotherapy	28	25
External beam radiotherapy	5	5
Performance status		
0	2	2
1	33	30
2	40	36
3	35	32
Bowel obstruction	9	8
Ascites at time of operation	58	53
Pathologic characteristics		
DPAM	55	50
Intermediate	18	16
PMCA	29	27
High-grade nonmucinous lesions	8	7

CS, cytoreduction surgery; IPHC, intraperitoneal hyperthermic chemotherapy; DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis.

TABLE 2. *Operative and perfusion data for patients undergoing CS and IPHC for peritoneal dissemination of appendiceal malignancies*

Characteristic	Data
Length of operation (min)	
Mean ± SD	626.7 ± 166.1
Range	300–1020
Resection status (n)	
R0	31
R1	17
R2a	22
R2b	25
R2c	15
Length of hyperthermic chemoperfusion (min)	
Mean ± SD	110 ± 21
Range	60–120
Median	120
Dose of MMC (mg)	
Mean ± SD	37 ± 5
Range	20–50
Median	40
Temperature of perfusate (°C)	
Mean ± SD	41 ± 1
Range	39–44
Median	41

CS, cytoreduction surgery; IPHC, intraperitoneal hyperthermic chemotherapy; MMC, mitomycin C.

RESULTS

Patients and Clinicopathologic Features

A total of 110 patients with peritoneal surface malignancy from appendiceal primary tumors underwent 116 IPHCs. Patient demographics and baseline data are listed in Table 1. The mean age was 52.2 ± 11.9 years (range, 25–88 years), with a slight female preponderance. Fifty-nine percent of the study participants had undergone previous laparotomy, whereas only 25% had received prior chemotherapy. Ninety-three percent of the patients had PMP, and the remaining 7% had high-grade malignancies, including nonmucinous adenocarcinoma, adenocarcinoid tumors, and carcinoid tumors.

The operative and perfusion data are summarized in Table 2. The length of the operation (range, 300–1020 minutes) was dependent on the extent and location of disease at exploration. The goal of the laparotomy for CS was to render the patient free of disease. This required lysis of all adhesions and omentectomy, and it required multivisceral resections in other instances. The mean MMC dose was 37 ± 5 mg, and the length of chemoperfusion averaged 110 ± 21 minutes. Adjustments in the dose of MMC or the length of chemoperfusion were made according to the likelihood of chemotherapy-related toxicity. The quantity of residual disease was recorded by the primary surgeon. The resection statuses of all patients undergoing IPHC for primary appendiceal tumors are listed in Table 2.

Morbidity and Mortality

The 30-day postoperative morbidity and mortality were 38% and 4%, respectively. The same-hospitalization mortality was 6%. Four patients in this study died of sepsis. Wound infection (n = 18), hematological toxicity (n = 16), sepsis (n = 9), respiratory failure (n = 11), anastomotic leak (n = 4), and enterocutaneous fistulas (n = 3) account for all of the postoperative complications in this cohort of patients. The median length of stay for this group of patients was 9 days.

Survival and Follow-Up

For the cohort of 110 patients with a median follow-up of 34.8 months, the median OS was 63.6 months. The 1-, 3-, and 5-year OS was 80%, 59%, and 53%, respectively (Fig. 1). The survival rates include operative mortality. A univariate analysis of clinicopathologic factors was performed to identify singularly significant prognostic factors associated with OS after CS and IPHC for peritoneal surface malignancy

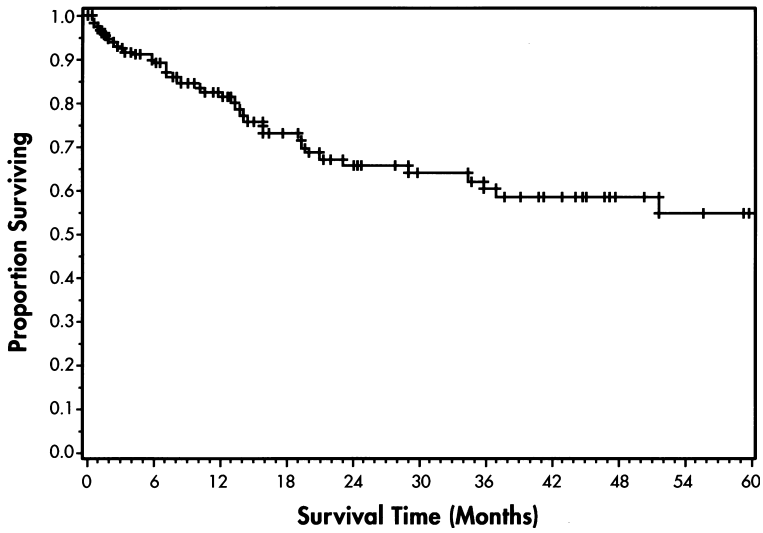

FIG. 1. Overall survival for patients treated with cytoreduction surgery and intraperitoneal hyperthermic chemotherapy for peritoneal dissemination of appendiceal neoplasms.

TABLE 3. *Univariate actuarial analysis of prognostic significance of clinicopathologic variables*

Variable of interest	*P* value
Race	.95
Dose of MMC	.91
Sex	.77
Previous chemotherapy	.52
Length of operation	.52
Previous debulking procedure	.49
Bowel obstruction	.42
Hepatic metastasis	.25
Age	.24
Time between diagnosis and IPHC	.23
Previous radiation	.19
Temperature of perfusate	.043
Length of chemotherapy	.021
Histological results	.0032
Performance status	.0001

MMC, mitomycin C; IPHC, intraperitoneal hyperthermic chemotherapy.

TABLE 4. *Prognostic significance of selected clinicopathologic variables based on multivariate stepwise regression analysis*

Variable	*P* value	HR	95% CI for HR
Length of chemoperfusion	.0193	.91	.83–.98
Age	.0134	1.04	1.01–1.08
Resection status	.0044	NA	—
Time between diagnosis and IPHC	.0011	.94	.92–.98
Performance status	<.0001	8.8	4.0–19.4

HR, hazard ratio; CI, confidence interval; NA, not available; IPHC, intraperitoneal hyperthermic chemotherapy.

from appendiceal primary tumors (Table 3). Multivariate analysis of factors affecting survival was performed via a stepwise regression technique. This analysis allowed for all variables regardless of their level of significance in the univariate analysis. The Cox proportional hazards regression model found that five clinicopathologic factors were independent predictors of OS: age at the time of perfusion, preoperative performance status, time between diagnosis of the appendiceal primary tumor and IPHC, resection status, and length of chemoperfusion. The *P* values and hazard ratios for these variables are summarized in Table 4; hazard ratios <1 indicate a protective effect for an increase in the measure. For example, the patients who received longer chemoperfusion times (as calculated in 5-minute increments) had longer survival than their counterparts who had shorter chemoperfusion times. Figures 2, 3, 4, and 5 depict the Kaplan-Meier actuarial survival curves for these factors.

DISCUSSION

There is a paucity of data regarding the utility of systemic therapy for appendiceal tumors. Therefore, the foundation of treatment for peritoneal dissemination of appendiceal malignancies remains aggressive surgical cytoreduction followed by hyperthermic peritoneal perfusion. Removal of bulk disease is imperative, because even the most ambitious perfusion strategies penetrate but 5 mm into the peritoneal surfaces. This aggressive cytoreduction allows hyperthermic chemoperfusion to treat the microscopic or small-volume residual disease.

Systemic chemotherapy for peritoneal surface malignancies is largely ineffective as a result of its

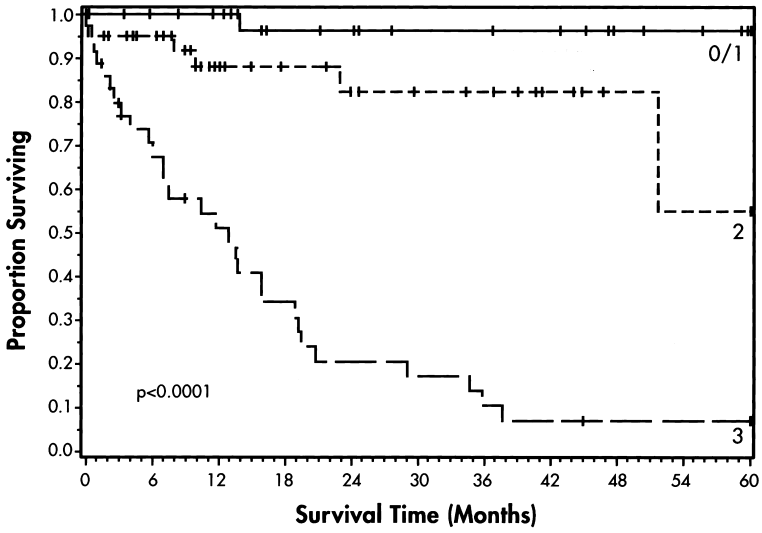

FIG. 2. Overall survival by preoperative performance status.

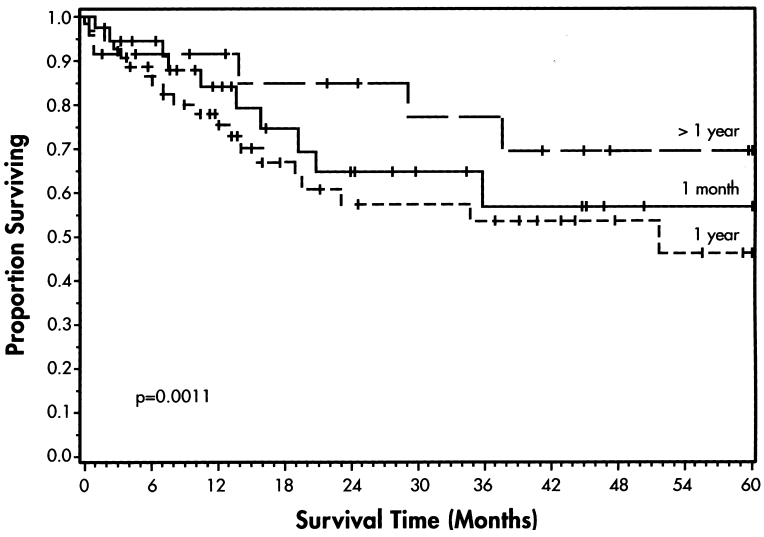

FIG. 3. Overall survival by time between diagnosis of the primary tumor and intraperitoneal hyperthermic chemotherapy.

limited entry into the peritoneum. The addition of intraperitoneal chemotherapy can be viewed as a tool to overcome the drug resistance associated with systemic administration. Systemic chemotherapy for intraperitoneal disease is largely ineffective for peritoneal surface malignancies because, at least in part, of the presence of a plasma-peritoneal partition. Early studies confirmed the presence of this peritoneal-plasma partition by demonstrating that drugs delivered into the peritoneal cavity have a clearance that is inversely proportional to the square root of its molecular weight.[9–11] Because of this partition, drugs without lipophilic properties and high molecular weights have optimal characteristics for intraperitoneal application. The pharmacokinetic advantage of intraperitoneal perfusion can be seen by the area under the curve ratios of peritoneal fluid to plasma that favor retention of drug in the peritoneum.[12–18] In addition to the pharmacokinetic advantage that intraperitoneal chemotherapy infusion after maximal tumor debulking offers, the addition of hyperthermia affects cell membranes, cytoskeletons, synthesis of macromolecules, and DNA-repair mechanisms.[19,20] Our institution has used MMC primarily. The synergy between MMC and hyperthermia occurs independently of the cell cycle, thus allowing for significant tumoricidal activity with brief exposures.[21] In this study, we evaluated various clinical, treatment, and pathologic characteristics that potentially affect survival for patients undergoing CS and IPHC with MMC for peritoneal surface malignancy from appendiceal neoplasms.

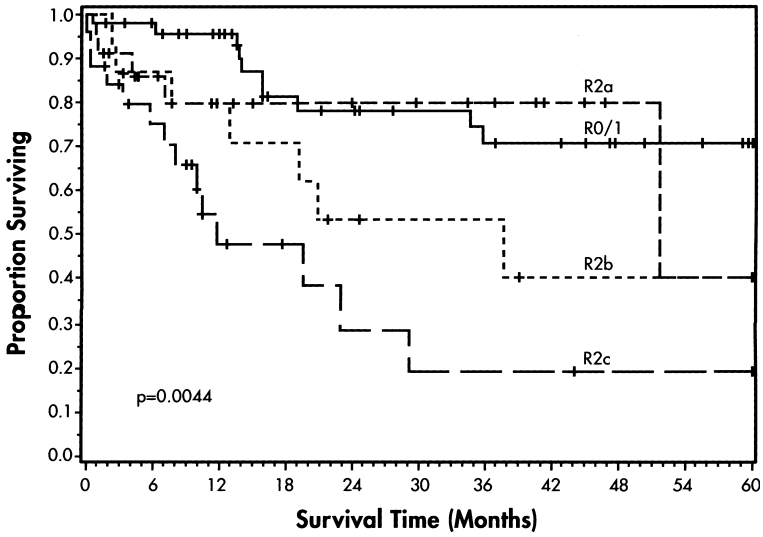

FIG. 4. Overall survival by resection status.

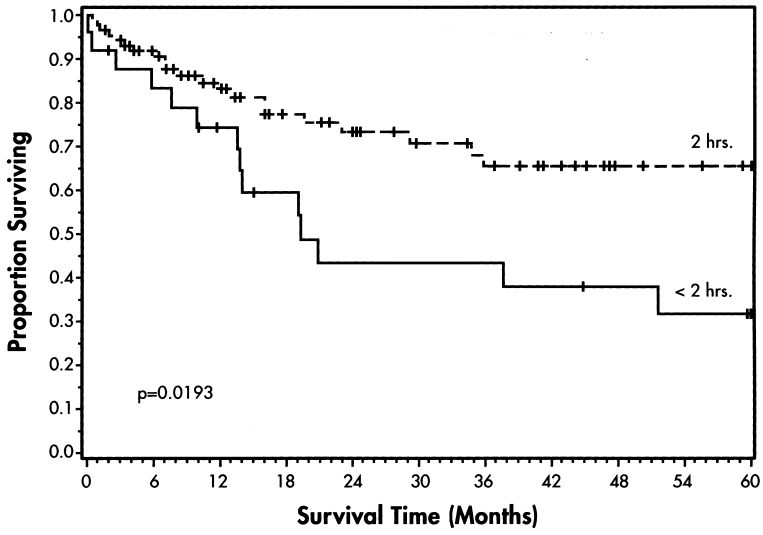

FIG. 5. Overall survival by length of hyperthermic chemoperfusion.

Pathologic characteristics clearly affect the clinical outcomes of patients with peritoneal surface malignancies from appendiceal primary tumors. In all surgical series, patients with PMP experience better clinical outcomes than those with nonmucinous appendiceal malignancies.[22,23] In this study, the 3-year survival rate in patients with high-grade nonmucinous lesions (i.e., appendiceal adenocarcinoma and adenocarcinoid and carcinoid tumors) was 15.0% ± 13.8%, whereas that for subgroups of PMP ranged between 81.5% ± 9.7% and 35.0 ± 10.3%. This is not an unexpected finding on the basis of the biological and molecular differences between PMP and high-grade nonmucinous appendiceal tumors. PMP does not typically metastasize beyond the abdominal/pelvic cavity. A recent correlative study found that appendiceal tumors associated with PMP have lower proliferative and apoptotic indices than colorectal epithelial neoplasms. Furthermore, PMP-producing tumors have decreased cell adhesion molecule expression.[24]

Pseudomyxoma peritonei has been considered the classic indication for IPHC. Five-year survival rates after IPHC for PMP have ranged between 66% and 97%.[25–28] Tumor histology is thought to be an independent prognostic factor in the subset of patients with PMP. The outcome with DPAM and intermediate/hybrid histology was significantly better than that of PMCA in the original description of the histological subtypes of PMP.[8] Later, data from the

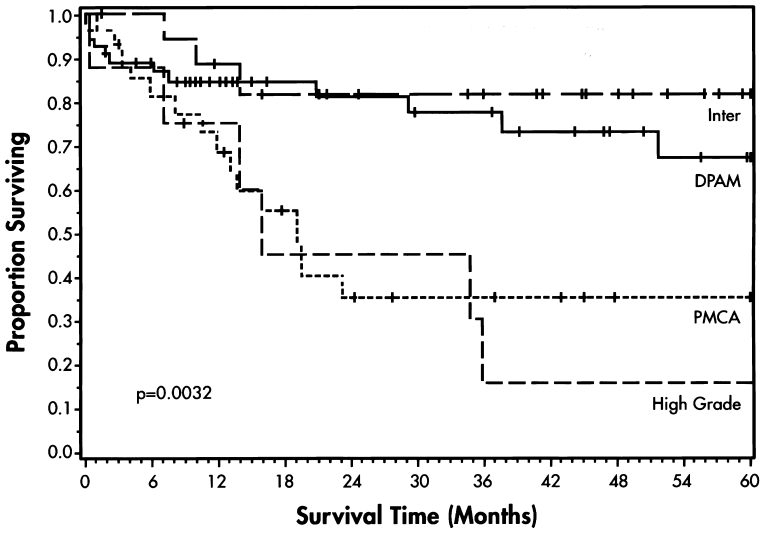

FIG. 6. Overall survival of patients with pseudomyxoma peritonei as stratified by histological characteristics. DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis.

Washington Hospital Center suggested that patients with DPAM had a better prognosis than those with mucinous adenocarcinoma or intermediate histology after exploratory laparotomy and cytoreduction.[25] A subsequent study revealed a difference in 5-year survival between DPAM (64%) and hybrid/PMCA (54%) with IPHC ($P = .05$). There were, however, very few PMCAs (3 of 36) in the follow-up study.[27] A criticism of past work evaluating CS and IPHC for PMP is that only benign or low-grade lesions were included in these studies. Hence, confounding factors such as tumor biology and patient selection were not accounted for in these prior studies. By using the system defined by Ronnett et al.,[8] patients in this study with PMP were further subclassified as having DPAM (55 of 102), intermediate (18 of 102), and PMCA (29 of 102) histological characteristics. The 3-year survival rates for DPAM and intermediate-grade PMP (77.4% ± 6.7% and 81.5% ± 9.7%, respectively) were superior to those for PMCA (35.0% ± 10.3%) and high-grade nonmucinous lesions (15.0% ± 13.8%; test of differences among groups, $P = .011$). This clearly demonstrates the differences in tumor biology among these histological subgroups of PMP (Fig. 6).

The heterogeneity of outcomes after therapy for PMP suggests that biological markers could be of significant clinical value. Mohamed et al.[29] evaluated mucin antigens MUC1 and MUC2 in an attempt to define the behavior of an aggressive variant of DPAM at a molecular level. However, no significant difference in the expression of these antigens was found in aggressive DPAM. It is interesting to note that current proteomics technology is capable of defining molecular signatures that depict tumor behavior and response to therapy with greater accuracy than current histopathologic methods. Future efforts by our group will focus on defining the molecular signatures of PMP and the correlation between histological findings and behavior in this group of patients.

Although tumor histological findings are strongly correlated with OS in the univariate model, Cox proportional hazards regression analysis did not indicate that tumor histology was an independent prognostic factor in a multivariate model with all other variables included at the outset of the model-fitting process. However, if performance status was removed from the regression model, tumor histology became a significant prognostic factor (Fig. 6). This suggests that performance status and tumor histology are surrogates that are related in this patient population. Subset analysis revealed that the high-grade tumors had worse performance status scores, because six of eight high-grade lesions had Eastern Cooperative Oncology Group (ECOG) scores of 3. The other histology groups tended to be more evenly dispersed across the performance status categories.

We reported in a prior study of patients with peritoneal carcinomatosis from a variety of histologies that patients with ECOG scores of 2 to 3 had significantly poorer OS (median survival of 9.5 months) than patients with ECOG scores of 0 or 1 (median survival of 21.7 months; $P = .02$).[7] This finding supports the use of CS and IPHC in patients who are medically fit to undergo such a large-scale procedure. In this study, preoperative performance status significantly affected survival after CS and

IPHC. In this cohort of patients, for each stepwise increase in ECOG score, the risk of death increased 8.8-fold. Patients with ECOG scores of 0 or 1 had not reached median survival, whereas those with ECOG scores of 2 or 3 had a median survival of 20.4 months ($P = .0001$). Therefore, we select patients for IPHC with ECOG scores of ≥2.

Patients undergoing complete CS before IPHC had superior outcomes compared with those who underwent incomplete CS. The 3-year survival rate for patients with an R0 resection was 69.4% ± 10.1%, whereas the 3-year survival rates for R1, R2a, R2b, and R2c resections were 74.1% ± 13.0%, 79.7% ± 9.2%, 18.9% ± 11.3%, and 39.7% ± 15.7%, respectively. This finding confirms data from our institution, and others, that demonstrate a significant survival advantage for patients undergoing R0/R1 resection compared with R2 resection.[7,30,31]

This study demonstrated a correlation between age and outcome after CS and IPHC for appendiceal malignancies in the multivariate analysis. The association between advanced age and shortened survival has been reported previously for appendiceal carcinoma. The reasons for this association are unclear. The finding is perhaps related to the differing age distribution for appendiceal malignancies.[32] In this study, for each 1-year of increase in age, the risk of death from appendiceal neoplasms increased by 4%. Unfortunately, this study does not differentiate between death from all causes and cancer-related deaths. Subset analysis of the data revealed that older patients tended to have shorter times of chemoperfusion and lower doses of MMC. Therefore, it is conceivable that selection bias, treatment effects, or a combination of these two factors could account for the association between age and outcome in older patients.

On multivariate analysis, an increasing time between diagnosis and IPHC resulted in better OS in this cohort of patients. In this study, for each additional month between the diagnosis of an appendiceal neoplasm and IPHC, the risk of death was reduced by 6%. Because appendiceal tumors tend to have protracted courses, it is expected that patients with longer intervals between diagnosis and IPHC tend to have less biologically aggressive tumors. These patients may also undergo multiple operative procedures before IPHC. This finding suggest that patients who have a long interval between diagnosis and ultimate treatment with IPHC might have good clinical outcomes despite the addition of hyperthermic chemoperfusion to CS.

Additionally, patients in this study who underwent longer periods of chemoperfusion had more favorable clinical outcomes. In this study, 24 patients underwent chemoperfusions of ≤90 minutes. According to the Cox proportional hazard model, for each additional 5 minutes of hyperthermic chemoperfusion in this patient population, the risk of death was reduced by 9%. The difference in survival is most likely related to selection and treatment effects because elderly individuals, those with extensive previous chemotherapy, those with inanition or poor performance status, and those undergoing extensive peritoneal stripping during surgery were often treated with shorter runs of chemoperfusion.

Several issues surround the future of IPHC in peritoneal dissemination from appendiceal malignancies. Chief among them is how to make such therapy standardized and available to large numbers of patients. At present there are approximately 25 active centers in the United States, and only half a dozen have experience of >100 cases. The operative procedures required for aggressive cytoreduction are lengthy, challenging, and morbid and use a great deal of hospital, blood bank, and surgical house officer resources. Further, the utilization (and safety) of chemotherapy in the operating room is daunting for many centers. Additionally, great care needs to be taken in selecting patients to undergo this procedure. It is estimated that only a handful of patients who are potential candidates for this therapy actually receive it; this is underscored by the relatively small number of patients accrued to the phase II studies for peritoneal carcinomatosis at large "perfusion centers." It is clear that expanding the number of centers should be performed by surgical oncologists who have more than a passing knowledge of systemic chemotherapy and are comfortable with the rigors of aggressive operative procedures in the abdomen.[6]

Although reported results from perfusion centers represent a substantial improvement in duration and, likely, quality of life,[33–35] most patients undergoing these procedures will experience tumor recurrence. Evaluating patients for second cytoreduction and additional chemoperfusion will become an ever more common problem because patients with PMP often require multiple procedures. We, and others, believe that in selected patients, a second cytoreductive procedure and chemoperfusion may be of value. In evaluating patients for second cytoreduction, the same criteria that are used to select patients for the first remain important. Specifically, the patients must remain medically fit to tolerate a major operative procedure, be free of extra-abdominal or hepatic parenchymal metastases, and have disease that seems amenable to complete cytoreduction. Additionally,

the time to recurrence after initial cytoreduction and the completeness of the initial cytoreduction should be considered in deciding whether to proceed with another procedure. Patients with bulk residual disease after an initial cytoreduction for appendiceal neoplasms should not be considered candidates for second cytoreductive procedures.[36] In this study, six patients underwent a second IPHC. These patients fulfilled all of the previously described criteria. The average time between the first and second perfusions was 2.11 ± .70 years. Five of the six patients were alive at the time of this manuscript preparation. The mean survival after the first perfusion was 4.3 ± 2.2 years, and the mean survival after the second perfusion was 2.5 ± 1.9 years after IPHC in the treatment of peritoneal surface malignancy from appendiceal neoplasms. However, several fundamental questions regarding IPHC in the setting of malignant peritoneal spread of appendiceal tumors need to be addressed. Foremost among these is whether the addition of IPHC after CS is of value. Clearly it would be desirable to evaluate, in a multicenter prospective randomized trial, the value of IPHC versus CS alone. However, such a multi-institutional study may prove difficult to complete. Dr. Richard Alexander and his group at the National Cancer Institute have initiated a phase III randomized study to evaluate the contribution of intraoperative and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from low-grade gastrointestinal adenocarcinomas. This trial is projected to accrue 82 patients over a 4-year period.

The advancement of centers of excellence and the initiation of cooperative group trials will help to define the optimal treatment approach for peritoneal spread from appendiceal neoplasms. The future of IPHC for appendiceal tumors lies in a multicenter and randomized trial that investigates not only response and survival, but also standardization of technique.

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