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Phase II Trial of Debulking Surgery and Photodynamic Therapy for Disseminated Intraperitoneal Tumors

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Background: Photodynamic therapy (PDT) combines photosensitizer drug, oxygen, and laser light to kill tumor cells on surfaces. This is the initial report of our phase II trial, designed to evaluate the effectiveness of surgical debulking and PDT in carcinomatosis and sarcomatosis.

Methods: Fifty-six patients were enrolled between April 1997 and January 2000. Patients were given Photofrin (2.5 mg/kg) intravenously 2 days before tumor-debulking surgery. Laser light was delivered to all peritoneal surfaces. Patients were followed with CT scans and laparoscopy to evaluate responses to treatment.

Results: Forty-two patients were adequately debulked at surgery; these comprise the treatment group. There were 14 GI malignancies, 12 ovarian cancers and 15 sarcomas. Actuarial median survival was 21 months. Median time to recurrence was 3 months (range, 1–21 months). The most common serious toxicities were anemia (38%), liver function test (LFT) abnormalities (26%), and gastrointestinal toxicities(19%), and one patient died.

Conclusions: Photofrin PDT for carcinomatosis has been successfully administered to 42 patients, with acceptable toxicity. The median survival of 21 months exceeds our expectations; however, the relative contribution of surgical resection versus PDT is unknown. Deficiencies in photosensitizer delivery, tissue oxygenation, or laser light distribution leading to recurrences may be addressed through the future use of new photosensitizers.

Key Words: Photodynamic therapy—Carcinomatosis—Sarcomatosis—Photofrin—Ovarian cancer.

Disseminated intraperitoneal tumor is a pattern of disease spread in gastrointestinal malignancies, ovarian cancers and sarcomas that often occurs in the absence of lymphatic or hematogenous metastases.[1,2] This disease often affects relatively young patients, but there is no established, curative therapy available. Systemic chemotherapy has a limited effect on this disease, and radiotherapy is not a viable option, because it would be necessary to treat the entire abdominal cavity, and toxicity would be excessive. Surgical resection alone is destined to fail because all peritoneal surfaces are contaminated with tumor. Even aggressive peritonectomy procedures leave large areas of the abdominal cavity untreated, including the capsules of the spleen and liver and the bowel serosa.[3] In ongoing clinical trials, aggressive surgical debulking has been combined with either intraperitoneal chemotherapy, immunotherapy, or hyperthermic peritoneal perfusion in an attempt to control this condition.

Photodynamic therapy (PDT) is a novel anticancer treatment that combines photosensitizer drug, oxygen, and laser light to kill tumor cells on surfaces.[4,5] The most common photosensitizer agent currently in use is Photofrin, a purified form of hematoporphyrin derivative (HPD). Its mechanism of action is the formation of oxygen free radical compounds after activation by a particular wavelength of light, resulting in direct cytotoxicity and microvascular damage.[6] The ideal photosensitizer localizes to tumor tissue in higher concentrations

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than in nearby normal tissues, and preclinical research with HPD and Photofrin has shown tumor localization of these compounds.[7] Although the photosensitizer drug is administered systemically, the cytotoxic effect is limited to those tissues exposed to the activating light dose. The depth of penetration varies with the wavelength of light, but usually is in the range of a few millimeters. Thus, PDT theoretically is an ideal therapy for the peritoneal surface disease that characterizes carcinomatosis and sarcomatosis. This therapy has been approved by the Food and Drug Administration (FDA) for treatment of obstructing esophageal and lung cancers, and is under study in cutaneous, bladder, pleural, and head and neck cancers, all of which are surface malignancies.

In the mid-1980s, preclinical work using Photofrin PDT in a mouse ovarian teratoma model of carcinomatosis resulted in cures of the otherwise lethal cancer.[8,9] Based on this preclinical work and toxicity studies in large animals, a Phase I trial at the National Cancer Institute enrolled 54 human patients with carcinomatosis and sarcomatosis.[10,11] Using escalating light and drug dosing, the dose-limiting toxicities were found to be bowel perforation and fistula formation. Laser wavelength and light and drug dose modifications, particularly in treating the bowel, resulted in acceptable toxicity. Although this Phase I trial was not designed to determine effectiveness, the patient outcomes were extremely suggestive of therapeutic benefit, with over 60% survival at 3 years and at least four patients with prolonged disease-free survival. This is the initial report of our phase II trial utilizing the maximal tolerated doses of photosensitizer and light defined in the Phase I trial, designed to evaluate the effectiveness of PDT in patients with carcinomatosis or sarcomatosis.

MATERIALS AND METHODS

Patient Selection

Fifty-six patients were enrolled in the trial between April 1997 and January 2000. Criteria for patient selection are outlined in Table 1. Patients with all tumor histologies and previous therapies were eligible for the trial, as long as there was no evidence of disease outside the peritoneal cavity or hematogenous liver disease. This was confirmed with clinical evaluation and CT scanning of the chest, abdomen, and pelvis or equivalent three-dimensional imaging. This trial was approved by the Institutional Review Board of the University of Pennsylvania, the Clinical Trials Scientific Review and Monitoring Committee of the University of Pennsylvania, and the United States Food and Drug Administration. All participating patients provided informed consent.

Treatment Protocol

The first step in patient treatment was intravenous administration of 2.5 mg/kg of Photofrin (QLT Phototherapeutics Ltd., Vancouver, British Columbia, Canada) 2 days before scheduled laparotomy. After drug administration, patients were instructed to avoid exposure to sunlight or non-fluorescent artificial light for 4 to 6 weeks. Before surgery, the operating room (OR) lights were covered with filters to prevent burning of exposed patient tissues, and the operating team was equipped with filtering glasses to be worn during laser light administration.

At laparotomy, tumor was debulked to a thickness of 5 mm or less. Organ resections required to achieve this debulking were performed, although nodules were resected from organ surfaces where feasible. Peritoneal stripping was performed as needed to remove gross tumor nodules but was not performed for microscopic disease. Complete lysis of adhesions was required to allow light delivery to all surfaces and to remove all gross disease wherever possible. Patients without diffuse carcinomatosis or patients whose tumors could not be debulked to 5 mm maximal tumor thickness did not receive laser light treatment and were considered to be off study.

Laser light was delivered to all peritoneal surfaces by the radiation oncology and physics staff using defined doses and wavelengths from the Phase I trial. First, 532-nanometer (nm) wavelength (green) light was administered to the small bowel, bowel mesentery, and

TABLE 1. *Patient selection criteria*

Inclusion Criteria	Exclusion Criteria
• Carcinomatosis or sarcomatosis of any history	• Hematogenous spread outside peritoneal cavity
• No curative treatment options available	• Intrahepatic metastases
• No evidence of extraperitoneal disease	• Tumors of borderline malignant potential
• Adequate renal and hematologic function	• Cirrhosis, Grade III–IV LFT elevations, or bilirubin >1.5
• Tumor able to be debulked to 5-mm residual tumor thickness before laser treatment	• Inflammatory bowel disease
• Re-treatment allowed (3)	• HIV

colon in segments at a dose (fluence) of 2.5 J/cm^2 using a flat-cut optical fiber (Laserscope Inc., San Jose, CA) suspended over the operating table. The light dose was monitored using a mobile photodiode held over the treatment area. Then the other peritoneal surfaces were treated with 630-nm (red) laser light delivered with a fiber enclosed in an intralipid-filled, modified endotracheal tube. The peritoneum also was filled with a solution of 0.01% intralipid containing calcium and magnesium, and the endotracheal tube was submerged within the solution. Care was taken to avoid contamination of the solution with blood, because this results in absorption of the laser light and reduction in the delivered dose rate. Five temporarily implanted photodiodes and one mobile photodiode were used to measure the light dose delivered to each peritoneal region. The fluences used for each area of the peritoneum were as follows: stomach, 5 J/cm^2; diaphragms, liver, and spleen, 7.5 J/cm^2; and pelvis and peritoneal gutters, 10 J/cm^2. Focal areas of the peritoneum with severe tumor involvement were treated with "boost" doses of 630-nm laser light. The laser equipment used consisted of a KTP/532 Laser System and a 630 $\times$ P Dye Module (Laserscope Inc., San Jose, CA).

After light treatment, the abdomen was copiously irrigated. Bowel anastomoses (if necessary) were performed at that time, and closure was completed. Postoperative care consisted of admission to the intensive care unit and close hemodynamic monitoring, with resuscitation as required. Perioperative toxicity was monitored using the National Cancer Institute (NCI) Cooperative Group Common Toxicity Criteria. Some delayed toxicities, such as small bowel obstruction and hydronephrosis, also were included in the toxicity analysis, especially if the toxicity necessitated readmission.

Patient Follow-up and Statistical Analysis

Patients were followed with clinical exams, computed tomography (CT) scans, and laparoscopy to evaluate responses to treatment. Patient follow-up visits were scheduled for 1 month and 3 months postoperatively, and every 3 months thereafter. CT scans were performed every 3 months, and laparoscopic evaluation was offered at the 6-month follow-up to every patient who was CT scan-negative for recurrence. Patients were considered "off study" at the time of radiographic or biopsy-proven recurrence, and alternative therapies were allowed thereafter. Retreatment with the PDT protocol was allowed for three patients who developed recurrences after a long disease-free interval. Only the first treatment of these retreated patients was included in this toxicity and outcome analysis. Time to recurrence and survival were analyzed using Kaplan-Meier survival curves. A Kaplan-Meier survival curve also was constructed comparing patients who had all gross disease resected versus those with residual gross disease before light therapy.

RESULTS

Patient Demographics

Fifty-six patients were entered into the trial between April 1997 and January 2000. Forty-three were able to be completely debulked and received laser light activation. Of this group, one patient's final pathology was negative for malignancy and consisted of bulky fibrosis that was benign; this patient was excluded from the treatment group for purposes of further analysis. The thirteen patients who did not undergo the full therapy included seven women and six men with the following histologies: six gastrointestinal (GI) cancers, three sarcomas, and four ovarian cancers. The reasons for exclusion from treatment were as follows: tumor unable to be debulked (ten patients); unsuspected liver metastasis (one patient); and only locally recurrent disease found at laparotomy (two patients).

The 42 patients who made up the treatment group are the focus of the following results. The average age of the treatment group was 48.8 years (range, 21–70 years). The gender distribution was 30 women and 12 men. Ninety-five percent had previous surgical resection, and over 60% had previous chemotherapy (data not shown). The histologies of the treatment group are displayed in detail in Table 2. When available, the pathology reports from the patients' initial surgical resection (often at another institution) were reviewed by our pathologists, and these results are shown. In several cases, the pathology report from our surgical resection was used. Fourteen patients had GI malignancies (colon [6 patients], appendiceal mucinous adenocarcinoma with malignant features [3 patients], gastric [2 patients], pseudomyxoma peritonei [1 patient], 1 poorly-differentiated carcinoma of unknown primary [1 patient], and adenocarcinoid [1 patient]), 12 patients had ovarian cancers, 15 patients had sarcomas. and 1 patient had peritoneal malignant mesothelioma.

Surgical Procedures Performed

The surgical procedures included a complete lysis of adhesions for all patients, plus a variety of organ resections to remove all gross disease. The organ resections performed are presented by percentage of patients affected in Fig.1. Peritoneal stripping was performed only where required to remove gross tumor nodules. When possible, all gross disease was resected.

TABLE 2. *Tumor histologies of the treatmentgroup*

Patient	Pathology Report
Gastrointestinal	
1	Appendiceal carcinoid with poorly differentiated adenocarcinoma
2	Mucinous adenocarcinoma of colon with positive lymph nodes
3	Poorly differentiated carcinoma with signet ring features of unknown primary
4	Mucinous adenocarcinoma involving cecum and appendiceal base
5	Well differentiated adenocarcinoma of colon with positive lymph nodes
6	Mucinous adenocarcinoma consistent with appendiceal primary, invading muscle of colon
7	Moderately differentiated gastric adenocarcinoma with positive lymph nodes
8	Poorly differentiated adenocarcinoma of colon with positive lymph nodes
9	Poorly differentiated gastric signet ring adenocarcinoma with positive lymph nodes
10	Mucinous appendiceal signet ring adenocarcinoma with positive lymph nodes
11	Poorly differentiated mucinous adenocarcinoma of colon with positive lymph nodes
12	Well differentiated appendiceal mucinous adenocarcinoma (pseudomyxoma peritonei)
13	Poorly differentiated adenocarcinoma of colon with positive lymph nodes
14	Moderately differentiated appendiceal mucinous cystadenocarcinoma
Mesothelioma	
15	Malignant intra-abdominal mesothelioma
Ovarian	
16	Papillary serous ovarian adenocarcinoma with positive lymph nodes
17	Poorly differentiated ovarian papillary adenocarcinoma
18	Poorly differentiated papillary serous ovarian cystadenocarcinoma
19	Poorly differentiated ovarian carcinoma
20	Poorly differentiated papillary serous ovarian adenocarcinoma
21	Poorly differentiated papillary serous ovarian adenocarcinoma with lymphatic invasion
22	Poorly differentiated ovarian carcinoma
23	Poorly differentiated primary peritoneal carcinoma
24	Poorly differentiated carcinoma
25	Poorly differentiated papillary adenocarcinoma
26	Primary peritoneal carcinoma with positive lymph nodes
27	Adenocarcinoma of unknown primary with positive lymph nodes
Sarcoma	
28	Small bowel leiomyosarcoma or malignant GIST
29	Malignant small bowel leiomyosarcoma consistent with aggressive GIST
30	Small bowel leiomyosarcoma or GIST
31	High-grade small bowel leiomyosarcoma
32	Malignant leiomyosarcoma or GIST
33	High-grade spindle cell sarcoma
34	High-grade uterine leiomyosarcoma with positive lymph nodes
35	High-grade spindle cell sarcoma, suggestive of dedifferentiated liposarcoma
36	Malignant synovial cell sarcoma
37	Uterine leiomyosarcoma
38	High-grade spindle cell sarcoma consistent with malignant GIST
39	High-grade endometrial sarcoma
40	High-grade sarcoma
41	High-grade spindle cell tumor consistent with leiomyosarcoma, malignant hemangiopericytoma, or GIST
42	Malignant GIST

GIST, gastrointestinal stromal tumor.

Outcomes

The median time since treatment (follow-up) is 18.5 months, and median survival has not been established, because 57% of patients are alive to date. Kaplan-Meier curves depicting the overall survival and survival by histologic group are shown in Fig. 2. Median actuarial survival is 21 months for all groups combined, with a trend toward longest survival in ovarian cancer and shortest in gastrointestinal cancers. The difference between broad histologic groups is not statistically significant. Recurrence data are depicted in Fig. 3. As shown, most patients have early evidence of recurrence by CT scan or laparoscopy, although many remain clinically well.

We qualitatively reviewed the outcome data to determine whether the pattern of disease (fewer or more numerous nodules or size of nodules), the number of organs involved, or completeness of surgical resection influenced the likelihood of a poorer outcome. Although there was no obvious association with regard to pattern of disease or organ resection, the inability to be debulked to the absence of gross disease is associated with poorer survival. In the group of patients who have died thus far, 89% were unable to be resected free of all gross disease.

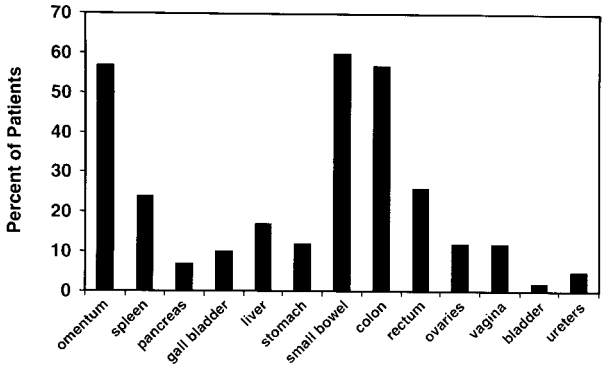

FIG. 1. Organ resections performed during debulking laparotomy in our treatment group, expressed as percentage of patients affected.

A Kaplan-Meier curve was used to plot the survival of the patients completely resected free of gross disease versus those with thin residual gross disease prior to light treatment. The patients who were completely resected before receiving PDT have a significantly better actuarial survival compared to patients who were incompletely resected (Fig. 4).

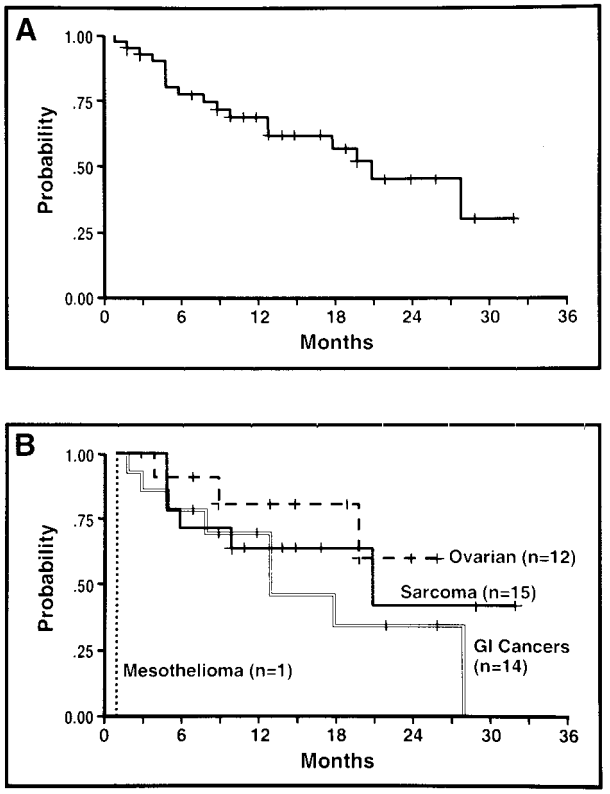

FIG. 2. Kaplan-Meier curves of fractional patient survival over time in our treatment group overall (**A**) and in each broad histologic group (**B**).

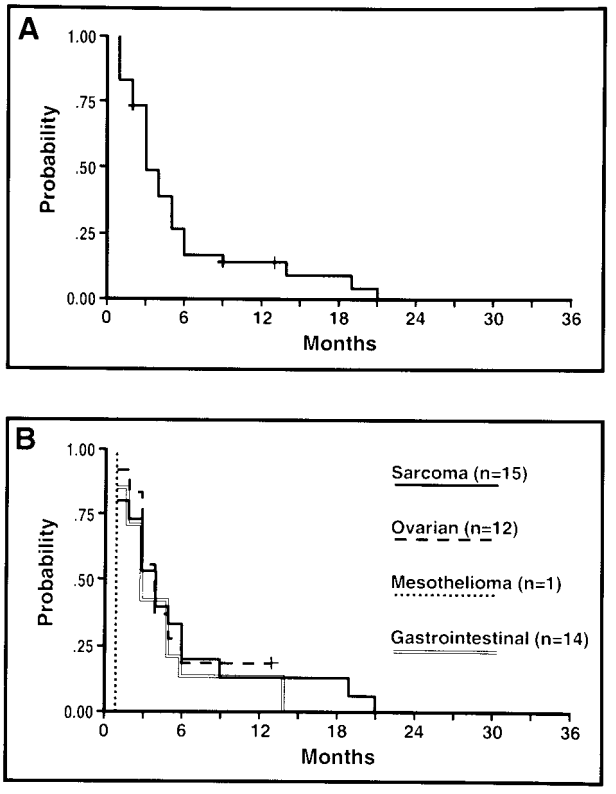

FIG. 3. Kaplan-Meier curves of overall time to recurrence in the treatment group overall (**A**) and in each broad histologic group (**B**).

Toxicity

Toxicity data are presented in Table 3. The most common serious (NCI Common Toxicity Criteria Grade 3–5) toxicities were anemia (38% of patients), transient LFT abnormalities (26%), and bowel obstruction or other GI abnormalities (19%). One patient died from a myocardial infarction early in our trial. One patient had a serious pulmonary embolism, three patients developed intra-abdominal abscesses, and two patients developed fistulae. There were no bowel perforations, although this was the primary dose-limiting toxicity in the Phase I trial. Patients required shielding from sunlight for 4 to 6 weeks due to residual photosensitizer effects; however, no serious skin toxicities occurred in follow-up. All patients developed the capillary leak syndrome perioperatively, characterized by a body weight gain of 15% to 20% and requiring intensive care management and volume resuscitation. In general, this syndrome resolved over the course of 3 to 7 days.

CONCLUSIONS

Meaningful treatment options are extremely limited for patients with disseminated intraperitoneal cancer.

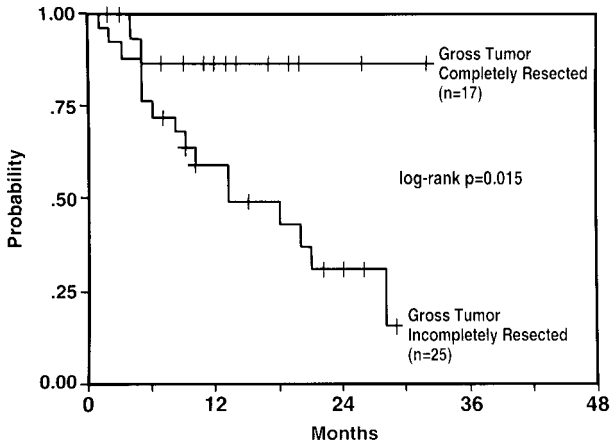

FIG. 4. Kaplan-Meier curve of survival comparing patients completely resected versus patients incompletely resected. This graph depicts the fraction of surviving treatment group patients over time divided into those patients completely resected free of gross disease vs. those patients unable to be completely resected free of all gross disease.

The patient population presented here is characterized by advanced disease, young age, and extensive previous treatment. For example, all but one of our ovarian cancer patients were treated in this study for recurrent carcinomatosis status-post previous debulking and chemotherapy. As can be seen from the table of treatment group histologies, only one patient in our treatment group had pseudomyxoma peritonei, which often has a very prolonged natural history. The other 41 patients in our treatment group had more aggressive histologies. The median survival of 21 months exceeds our expectations for this patient population.

TABLE 3. *Toxicities in treatment group (n = 42)*

Toxicity	Grade 1–2	Grade 3—5
	(No.)	No. (%)
Anemia	26	16 (38)
LFT abnormalities	20	11 (26)
Gastrointestinal	6	8 (19)
Hypotension	5	5 (12)
Edema	28	4 (10)
Hyperglycemia	30	4 (10)
Infection	13	4 (10)
Hypocalcemia	21	3 (7)
Abnormal PT/PTT	30	2 (5)
Thrombocytopenia	29	2 (5)
Fistula	—	2 (5)
Cardiac	1	2[a] (5)
ARDS	—	2 (5)
Hydronephrosis	8	1 (2)
Neurologic	4	1 (2)
PE or DVT	4	1 (2)
Pleural effusion	17	1 (2)
Fever	30	—
Skin	5	—
Creatinine elevation	4	—

[a] One patient death from myocardial infarction.

ARDS, adult respiratory distress syndrome; DVT, deep venous thrombosis; LFT, liver function test; PE, pleural effusion; PT, prothrombin time; PTT, partial thromboplastin time.

Although most of these patients have recurred, many are clinically well for long intervals after therapy, and several have had prolonged disease-free survival. Our aggressive approach for identifying early recurrences, i.e., CT scans every 3 months and laparoscopy at 6 months, has contributed to our large proportion of early recurrences. For example, one patient with colon cancer had peritoneal implants smaller than 5 mm at 6-month laparoscopy, but at 26 months of follow-up is still clinically well. Nonetheless, this patient is counted as a 6-month recurrence.

The toxicity profile of our treated patients compares favorably with the toxicities seen from extensive debulking procedures in general and other experimental treatments for carcinomatosis in particular.[2,3] The most common serious toxicities were anemia, transient LFT abnormalities, and bowel obstruction or other GI abnormalities. The one treatment death occurred in one of our earliest patients due to an acute myocardial infarction. Thereafter, with aggressive pretreatment cardiac screening, our cardiovascular morbidity has been minimal. Many of our toxicities can be related directly to the organ resections performed or to the underlying diagnosis of malignancy, such as the incidence of DVT, PE, diarrhea, and transient metabolic and hemodynamic abnormalities.

The toxicities that can be attributed specifically to the photodynamic therapy include (1) the capillary leak syndrome, with its attendant perioperative requirement for volume resuscitation and (2) the elevated frequency of hydronephrosis, which may be due to retroperitoneal scarring from the therapy. It is worth noting that there were no bowel perforations, given that this was the primary dose-limiting toxicity in the Phase I trial, although there were two fistulas. It is also worth commenting that no serious skin toxicities have occurred in follow-up, despite the long half-life of our current photosensitizer agent.

The obvious limitation in interpretation of these data is the lack of a debulking-only control group. Unfortunately, we must rely on historical data in order to determine whether our survival exceeds that expected for this population of patients. Limited data are available regarding this patient population, partly because debulking surgery is not routinely performed except in ovarian cancer, and partly because this patient population has an extremely heterogeneous natural history. Several recent studies focusing on carcinomatosis from gastrointestinal primaries have attempted to characterize the natural history of this disease.[1,2] Medial survivals of 3.1 to 6.7 months were reported for patients with carcinomatosis,

but some patients with hematogenous metastases were included in these analyses. Our patient population is exceedingly heterogeneous due to the open enrollment criteria for this trial, and future reports likely will focus on subgroup analysis in an effort to direct this therapy to those patients most likely to benefit. These early data reveal an association between the ability to be completely resected free of gross disease and survival, but it fails to reveal a survival advantage for any broad histologic group.

So far, our outcome analysis has focused on disease-free interval and survival; however, these may not be the most appropriate outcome measures for our patient population. Although we have not yet formally evaluated PDT as a palliative therapy, many of our patients have experienced an improved quality of life after hospital discharge, in terms of gastrointestinal function, resolution of ascites, improved energy level, and overall sense of well being. Obviously the toxicity of the procedure must be weighed against the benefits observed, and a formal evaluation of non-survival outcomes should be undertaken.

Several other trials are underway using local therapies for disseminated intraperitoneal cancer.[3,12–16] Investigators conducting trials with hyperthermic peritoneal perfusion, radical peritonectomy, intraperitoneal chemotherapy, and intraperitoneal immunotherapy also are approaching carcinomatosis and sarcomatosis as a "surface problem." Loggie and colleagues recently have reported the results of mitomycin C hyperthermic peritoneal perfusion following surgical debulking in 84 patients with gastrointestinal carcinomatosis.[16] Their results are remarkably similar to ours; they found an overall median survival of 14.3 months and improved survival in those patients able to be completely resected. These encouraging results validate the surgical oncology community's ongoing efforts to aggressively treat carcinomatosis with surface modalities.

In summary, Photofrin PDT for carcinomatosis has been successfully administered to 42 patients in our phase II trial, with acceptable toxicity. The median survival of 21 months exceeds our expectations, given the aggressive diseases of our patient population; however, the relative contribution of surgical resection versus photodynamic therapy is unknown. Disease recurrences may be due to deficiencies in photosensitizer delivery or localization, tissue oxygenation, or laser light distribution. Ongoing research in the preclinical setting is addressing these issues with new, "second generation" photosensitizer agents. These agents will have a shorter half-life and better tumor localization, potentially overcoming our current limitations.

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