Intraperitoneal Chemotherapy for Peritoneal Surface Malignancy: Experience with 1,000 Patients

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BACKGROUND: Peritoneal dissemination of abdominal malignancy (carcinomatosis) has a clinical course marked by bowel obstruction and death; it traditionally does not respond well to systemic therapy and has been approached with nihilism. To treat carcinomatosis, we use cytoreductive surgery (CS) with hyperthermic intraperitoneal chemotherapy (HIPEC).

METHODS: A prospective database of patients has been maintained since 1992. Patients with biopsy-proven peritoneal surface disease were uniformly evaluated for, and treated with, CS and HIPEC. Patient demographics, performance status (Eastern Cooperative Oncology Group), resection status, and peritoneal surface disease were classified according to primary site. Univariate and multivariate analyses were performed. The experience was divided into quintiles and outcomes compared.

RESULTS: Between 1991 and 2013, a total of 1,000 patients underwent 1,097 HIPEC procedures. Mean age was 52.9 years and 53.1% were female. Primary tumor site was appendix in 472 (47.2%), colorectal in 248 (24.8%), mesothelioma in 72 (7.2%), ovary in 69 (6.9%), gastric in 46 (4.6%), and other in 97 (9.7%). Thirty-day mortality rate was 3.8% and median hospital stay was 8 days. Median overall survival was 29.4 months, with a 5-year survival rate of 32.5%. Factors correlating with improved survival on univariate and multivariate analysis (p < 0.0001 for each) were preoperative performance status, primary tumor type, resection status, and experience quintile (p = 0.04). For the 5 quintiles, the 1- and 5-year survival rates, as well as the complete cytoreduction score (R0, R1, R2a) have increased, and transfusions, stoma creations, and complications have all decreased significantly (p < .001 for all).

CONCLUSIONS: This largest reported single-center experience with CS and HIPEC demonstrates that prognostic factors include primary site, performance status, completeness of resection, and institutional experience. The data show that outcomes have improved over time, with more complete cytoreduction and fewer serious complications, transfusions, and stomas. This was due to better patient selection and increased operative experience. Cytoreductive surgery with HIPEC represents a substantial improvement in outcomes compared with historical series, and shows that meaningful long-term survival is possible for selected carcinomatosis patients. Multi-institutional cooperative trials are needed to refine the use of CS and HIPEC. (J Am Coll Surg 2014;218:573–587. © 2014 by the American College of Surgeons)
pathologic lesions. Such findings are all too common for gastrointestinal and ovarian carcinomas, and are also seen with unusual malignancies, such as sarcoma, mesothelioma, and urachal carcinoma.

Frequently, PSD is confined to the peritoneal cavity without extra-abdominal disease. Therefore, a regional approach to selected patients with PSD is reasonable. In the 1980s, aggressive multimodality treatment of peritoneal surface malignancies was attempted to improve outcomes. Centers explored treatment options such as peritonectomy procedures, intraoperative injection of 32P, immunotherapy, photodynamic therapy, hyperthermic intraperitoneal chemotherapy (HIPEC), and early postoperative intraperitoneal chemotherapy. During the past 2 decades, there has been ever-increasing interest in such regional therapy for PSD. This has been stimulated by publication of a prospective randomized trial for PSD from colorectal sources, as well as successes with ovarian cancer.

The optimal management of patients with PSD remains a matter of debate. Systemic chemotherapy for PSD is limited, in part, by its restricted ability to enter the peritoneal cavity. The localization of tumor within the peritoneum without distant metastasis makes an aggressive regional approach attractive. Several groups have treated peritoneal surface dissemination of appendiceal tumors with debulking procedures. However, these procedures are frequently unable to remove all of the microscopic tumor.

Our approach to selected patients with PSD has been to combine aggressive CS (with the goal or resection of all gross disease) with chemoperfusion to address microscopic residual. Because surgery alone cannot address such microscopic residual, we have used intraoperative intraperitoneal chemotherapy as an adjuvant. An intraoperative chemotherapy perfusion done at the same time as CS has several advantages: first, intracavitary chemotherapy achieves drug levels far higher than can be obtained with even the most aggressive systemic administration, which can overcome relative drug resistance; next, after CS, all peritoneal surfaces are exposed (all adhesions lysed), which allows for better drug distribution (vs postoperative). Additionally, the single intraoperative dose eliminates the considerable compliance/tolerance issues encountered with postoperative administration of several cycles of treatment.

The rationale for hyperthermia is based on laboratory studies showing synergy with certain drugs, and it has the advantage of avoiding hypothermia, which is frequently encountered with prolonged open procedures.

We have previously reported our experience as well as subsets of patients treated with CS and HIPEC for PSD from appendiceal, colorectal, gastric, small bowel, and urachal carcinomas, as well as sarcomatosis and mesothelioma. Here we examine our experience with patients undergoing CS and HIPEC for PSD to evaluate our outcomes with the first 1,000 patients.

**METHODS**

Patients who underwent CS and HIPEC for PSD at Wake Forest University School of Medicine Baptist Hospital between 1991 and 2013 were identified from a prospective database. This database has been continuously approved by the Institutional Review Board at Wake Forest University. Clinical data on all patients were recorded in the database and maintained by a dedicated data management unit. All patients were evaluated in the Surgical Oncology Clinics preoperatively. Evaluations included, at a minimum, a complete history, examination, pathologic review, CT or MRI imaging, blood counts, and renal and liver functions. To be considered for CS and HIPEC, patients needed to have normal organ function (serum creatinine <3 mg/dL, alkaline phosphatase and serum aspartate transaminase or alanine transaminase <3 times the upper limit of normal, white blood cell count ≥4,000/mm³, and platelet count ≥100,000 mm³). Evaluation of preoperative CT or MRI imaging focused on the absence of extra-abdominal metastasis, parenchymal hepatic metastasis (limited, completely resectable and hepatic and liver surface lesions allowed), bulky small bowel disease, multi-station bowel obstruction, ureteral, or biliary obstruction. Tumors were categorized according to the primary site of origin. Before CS and HIPEC, patients had their pathology reviewed by the Wake Forest University Department of Pathology. This was compared with final pathology from specimens garnered at the time of CS to reach a final diagnosis for the database. Patients with bulky pelvic disease or multiple previous pelvic procedures were routinely considered for urologic consultation for cystoscopy, with temporary externalized ureteral stent placement at the start of the procedure to facilitate retroperitoneal and pelvic dissection. Morbidity was defined according to the Clavien-Dindo classification system. Postoperative mortality was assessed at 30 days after the procedure. The clinical experience was divided.

Cytoreductive surgery

The goal of CS was removal of all gross disease in all cases. Cytoreductive surgery consisted of the removal of gross tumor and involved organs, peritoneum, or tissue deemed technically feasible and safe for the patient. On opening the abdomen, the quantity and distribution of disease and/or ascites present was noted and quantitated (since 2005) by the peritoneal carcinomatosis index. This included routine supracolic omentectomy in all cases where it was not performed previously. Peritonectomy procedures were performed only as indicated by the presence of visible disease. Any tumors adherent or invasive to vital structures that could not be removed were cytoreduced using standard techniques or the cavitational ultrasonic surgical aspirator. The resection status of patients was judged after CS 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 post-perfusion cytological findings or microscopic margins; R2a, minimal residual tumor, nodule(s) measuring ≤0.5 cm; R2b, gross residual tumor, nodule >0.5 cm but ≤2 cm; and R2c, extensive disease remaining, nodules >2 cm.

Intraperitoneal hyperthermic chemotherapy

Near the completion of CS, the patient was cooled to a core temperature of approximately 34°C to 35°C by passive measure (ie, not warming airway gases or intravenous solutions and cooling the room). Constant patient and perfusate temperature monitoring was performed in all cases. After CS was completed, peritoneal perfusion was facilitated via two 22F inflow and two 32F outflow catheters placed percutaneously into the abdominal cavity. Temperature probes were placed on the inflow and outflow tubing and were continuously monitored. 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 crystalloid (typically Ringer’s lactate or plasmalyte). Flow rates of approximately 1 L/min were maintained using a roller pump managed by a perfusionist. The circuit continued through a single roller pump, through a heat exchanger, and then to the patient. Once a stable perfusion circuit was established and outflow temperature was >38.5°C, the chemotherapy was introduced into the perfusion circuit. A maximum inflow temperature of 43°C was tolerated 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. Total planned perfusion time after the initial addition of chemotherapy was typically 120 minutes. Although several chemotherapeutic agents were used, most patients received mitomycin c (MMC). The MMC was dosed based on volume of perfusate necessary to establish a stable circuit (typically 3 L). When MMC was used, 30 mg was added to the perfusate at the initiation of the HIPEC, and at 60 minutes an additional 10 mg MMC was added to keep MMC perfusate concentrations >5 μg/mL. In certain patients (eg, elderly individuals, those with extensive previous chemotherapy, poor performance status), reductions in the dose of MMC (to 30 mg total) or perfusion time (to 60 to 90 minutes) were made to minimize hematotoxicity. Other chemotherapeutic agents were also used based on primary tumor site and previous systemic therapy. Since 2004, we have used cisplatin 250 mg/M² with sodium thiosulfate for mesothelioma cases. Ovarian cases used cisplatin or carboplatinum (1,000 mg/M²). Sarcoma cases (and gastrointestinal stromal tumor before the introduction of imatinib) were perfused with MMC with or without mitoxantrone. We also used oxaliplatin (200 mg/M²) for select appendical and colonic cases.

Clinical follow-up

Clinical follow-up occurred at 1 month and then at least every 6 months thereafter for up to 5 years. After 5 years from the last HIPEC, follow-up was suggested on an annual basis. Blood counts, liver functions, and tumor markers (as appropriate), as well as abdominal and pelvic CT or MRI scans with intravenous contrast, were obtained with each follow-up visit and when clinically indicated. Patients were typically followed jointly with medical oncologists. Some patients received systemic chemotherapy at the discretion of their medical oncologists. Of the first 1,000 patients on the HIPEC database, 78 were lost to follow-up (7.8%). The longest survivor after HIPEC underwent the procedure 225 months ago.

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. Overall survival (OS) was calculated from the date of CS and
HIPEC to the last known date of follow-up or date of death. Estimates of survival were calculated using the Kaplan-Meier (product-limit) method; analysis using Cox proportional hazards was performed on all pertinent clinicopathologic variables to determine each one’s association with survival. Group comparisons of OS were performed using the approximate chi-square 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 \( p \leq 0.05 \).

**RESULTS**

**Patients and clinicopathologic features**

A total of 1,000 patients underwent 1,097 HIPEC procedures between December 30, 1991 and June 10, 2013. This study was approved by our Institutional Review Board. Patient outcomes data stratified by experience quintiles are listed in Table 1. Mean age was 52.9 ± 12.4 years (range 11 to 87 years of age); 53.1% were female. Median ICU and hospital stays are currently 1 and 8 days, which has decreased significantly from 2 and 9 days in the first quintile \( p = 0.03 \) and \( p < 0.0001 \), respectively (Table 1). As part of the CS, 19.0% of patients had an ileostomy (12%) or colostomy (7%) created. However, the frequency of stoma placement has decreased considerably over time. The organs resected as part of the CS are listed in Table 2. Most (68%) of the patients had received systemic chemotherapy before HIPEC. Median hospital stay was 9 days, with a mean of 14.1 days (±16.3 days). Most (73%) patients were admitted to the ICU with a mean stay of 1 to 2 days, with a decrease in ICU stay found over time.

Primary sites of origin for the patients were as follows: adrenal, \( n = 2 \) (0.2%); appendix, \( n = 472 \) (47.2%); colorectal, \( n = 248 \) (24.8%); gallbladder, \( n = 5 \) (0.5%); gastric, \( n = 46 \) (4.6%); gastrointestinal stromal tumor, \( n = 9 \) (2%); liver, \( n = 2 \) (0.2%); mesothelioma, \( n = 72 \) (7.2%); ovary, \( n = 66 \) (6.9%); pancreas (cystic neoplasm and IPMT), \( n = 6 \) (0.6%); sarcoma, \( n = 14 \) (1.4%); small bowel, \( n = 17 \) (1.7%); urachal, \( n = 5 \) (1.1%); and unknown, \( n = 19 \) (1.9%). Median survival was significantly different by site of origin as follows: appendix, 63.5 months; colorectal, 16.4 months; gastric, 6.1 months; mesothelioma, 27.1 months; ovary, 28.5 months; and sarcoma, 28.1 months (\( p = 0.0001 \)). For other histologic sites of origin, the series has too few cases for meaningful analysis. The distribution of the primary sources of PSD has changed over time, with increases in appendiceal primary cases and decreases in gastric and sarcoma cases.

Operative and perfusion data are summarized in Table 1. Mean peritoneal carcinomatosis index was 12. Length of the operation (range 183 to 1,531 minutes) was dependent on the extent and location of disease at exploration, but averaged just <10 hours. The quantity of residual disease was recorded by the primary surgeon and was scored according to the R status for residual disease. The R status of all patients undergoing HIPEC is listed in Table 1. The resection status was a significant predictor of survival (\( p < 0.0001 \)). For the purposes of survival calculations, R0 and R1 were combined because of difficulties in clearly separating them (as radial margins are typically positive) in the setting of PSD.

**Morbidity and mortality**

The 30-day postoperative morbidity and mortality were 42% and 3.8%, respectively. Thirty-eight patients in this study died within 30 days of HIPEC. Wound infection, hematologic toxicity, sepsis, respiratory failure, anastomotic leak, pneumonia, and enterocutaneous fistula account for the majority of the postoperative complications in this cohort of patients. The mortality rates did not change significantly by quintile and range from 2.5% (fifth quintile) to 6% (second quintile). Patients who experienced a complication had poorer survival than those who did not (\( p < 0.0001 \)). This difference remained significant on multivariate analysis. Complications were less common in patients undergoing R0/1 resections when compared with cases with more residual (\( p = 0.04 \)).

**Experience over time**

To evaluate our experience over time, we divided our patient experience into 5 time periods (quintiles) of 200 patients each. Median survival times for the 5 quintiles are 16.4, 28.5, 40.7, 34.3+, and 22.9+ months, respectively (\( p = 0.006 \) (Fig. 1). However, median length of stay was evenly distributed over the quintiles at 9, 10, 8, and 9 days, respectively. Mean (±SD) length of stay was 14.7 (±17.7), 15.3 (±17.9), 17.0 (±20.3), 12.1 (±13.1), and 13.2 (±13.7) days, respectively (\( p = 0.048 \)). The middle quintile is significantly higher than the fourth (\( p = 0.005 \)) and the last (\( p = 0.028 \)).

Selection of patients changed significantly during the experience, with increased rates of appendiceal (\( p < 0.0001 \)) and ovarian (\( p = 0.0005 \)) primary cases, and decreases in gastric (\( p < 0.0005 \)) and sarcoma (\( p = 0.02 \)) cases. Rates over time for mesothelioma and colonic cancer primary have not changed significantly. The rate of colostomy and ileostomy varied significantly over the
time quintiles (p = 0.0003 and p = 0.0009, respectively). The rate of complications varied significantly over the experience quintiles, with the highest rate during the third quintile (p < 0.0001). Median hospital and ICU stays decreased over time (p = 0.03 and p < 0.0001, respectively).

The mortality rate ranged from 2.6% to 7.0% during the 5 quintiles without significant differences. The rate of complete resection (as defined by R0, R1, or R2a) increased with each quintile (55.0%, 74.0%, 76.4%, 83%, and 88.3%, respectively; p < 0.001). Class IV and V complications decreased over time (45.0%,

Table 1. Clinicopathologic Data for 1,000 Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Surface Disease

<table>
<thead>
<tr>
<th>Clinicopathologic data</th>
<th>Quintile</th>
<th>Quintile</th>
<th>Quintile</th>
<th>Quintile</th>
<th>Quintile</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendix (n = 472)</td>
<td>56 (28)</td>
<td>80 (40)</td>
<td>116 (58)</td>
<td>121 (60.5)</td>
<td>99 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Colon (n = 232)</td>
<td>58 (29)</td>
<td>50 (25)</td>
<td>40 (20)</td>
<td>40 (20)</td>
<td>44 (22)</td>
<td></td>
</tr>
<tr>
<td>Gastric (n = 46)</td>
<td>27 (13.5)</td>
<td>12 (6)</td>
<td>3 (1.5)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma (n = 72)</td>
<td>12 (6)</td>
<td>13 (6.5)</td>
<td>12 (6)</td>
<td>12 (6)</td>
<td>23 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Ovary (n = 69)</td>
<td>18 (9)</td>
<td>25 (12.5)</td>
<td>5 (2.5)</td>
<td>8 (4)</td>
<td>13 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Others (n = 109)</td>
<td>29 (14.5)</td>
<td>20 (10)</td>
<td>24 (12)</td>
<td>17 (8.5)</td>
<td>19 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>92 (46)</td>
<td>76 (38)</td>
<td>49 (24)</td>
<td>90 (45)</td>
<td>115 (58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transfusion, n (%)</td>
<td>108 (54)</td>
<td>124 (62)</td>
<td>151 (76)</td>
<td>110 (55)</td>
<td>85 (42)</td>
<td></td>
</tr>
<tr>
<td>Stoma, n (%)</td>
<td>160 (88.4)</td>
<td>141 (70.5)</td>
<td>160 (80.0)</td>
<td>159 (79.5)</td>
<td>193 (86.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>ECOG, n (%)</td>
<td>97 (54.8)</td>
<td>47 (31.1)</td>
<td>60 (31.7)</td>
<td>69 (34.8)</td>
<td>45 (23.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resection, n (%)</td>
<td>71 (35.5)</td>
<td>93 (46.5)</td>
<td>103 (51.8)</td>
<td>93 (46.5)</td>
<td>104 (52.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clavien-Dindo, n (%)</td>
<td>59 (30.6)</td>
<td>72 (36.0)</td>
<td>59 (29.5)</td>
<td>65 (32.5)</td>
<td>39 (29.8)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Median hospital LOS, d</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>0.03</td>
</tr>
<tr>
<td>Median ICU LOS, d</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; LOS, length of stay.
26.0%, 23.6%, 17.0%, and 11.7%, respectively; \( p < 0.001 \). Rates of stoma creation (ileostomy or colostomy) decreased over time (11.8%, 29.5%, 20.0%, 20.6%, and 15.1% respectively; \( p < 0.001 \)). In addition, the 1- and 5-year OS rates have increased over time (with the 5-year median OS not yet reached for the latest 2 quintiles).

For the cohort of 1,000 patients with a median follow-up of 54.1 months, median OS was 29.4 months. One, 3-, 5-, 10-, and 15-year OS rates (±SE) were 72.3% (±1.5%), 44.6% (±1.7%), 31.5% (±1.8%), 18.1% (±1.9%), and 10.7% (±2.7%), respectively (see Figs. 1 to 5). Second HIPEC was performed on 89 selected patients for recurrent/persistent disease,30 with 8 subjects undergoing 3 procedures. When plotting the overall survival time after repeat vs initial HIPEC, the results are strikingly similar (Fig. 6). 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 HIPEC for PSD. Multivariate analysis of factors effecting survival was performed via a stepwise regression technique. This analysis allowed for all variables regardless of level of significance in the univariate analysis. The Cox proportional hazards regression model found that 5 clinicopathologic factors were independent predictors of OS: tumor histology, resection status, complications, and performance status (Table 3). Figures 1 to 6 depict the Kaplan-Meier actuarial survival curves for these factors.

### DISCUSSION

Cytoreductive surgery and HIPEC represent a substantial operative undertaking for both patient and surgeon. Mean operative times are approximately 10 hours, with ICU and hospital stays that consume substantial resources. Morbidity and mortality have improved over time but remain significant; straightforward preoperative discussions with the patient and family are, therefore,

#### Table 2. Listing of Organs Resected as Part of the Cytoreductive Surgery in Addition to Peritoneal Resections

<table>
<thead>
<tr>
<th>Organ resected</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm</td>
<td>98</td>
<td>9.8</td>
</tr>
<tr>
<td>Colon</td>
<td>500</td>
<td>50.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>78</td>
<td>7.8</td>
</tr>
<tr>
<td>Small bowel</td>
<td>322</td>
<td>32.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>111</td>
<td>11.1</td>
</tr>
<tr>
<td>Spleen</td>
<td>416</td>
<td>41.6</td>
</tr>
<tr>
<td>Uterus</td>
<td>91</td>
<td>17.1</td>
</tr>
<tr>
<td>Ovaries</td>
<td>170</td>
<td>32.0</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>291</td>
<td>29.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>62</td>
<td>6.2</td>
</tr>
<tr>
<td>Appendix</td>
<td>102</td>
<td>10.2</td>
</tr>
<tr>
<td>Omentum</td>
<td>717</td>
<td>71.7</td>
</tr>
<tr>
<td>Kidney</td>
<td>12</td>
<td>1.2</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>102</td>
<td>10.2</td>
</tr>
<tr>
<td>Bladder</td>
<td>25</td>
<td>2.5</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Umbilicus</td>
<td>27</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Omentectomy (supracolic) was performed routinely if not previously resected.

†Percentage of female patients.

![Figure 1](image1.png) Overall survival by quintile of experience, difference significant (\( p = 0.0006 \)).

![Figure 2](image2.png) Overall survival for 1,000 patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.
necessary. However, properly selected patients have a real chance at long-term survival that is rarely, if ever, realized without such aggressive efforts. Clearly, long-term survival is possible for patients with PSD. In our experience, we have modified our approach to PSD in terms of patient selection and, to a lesser extent, operative techniques.

Systemic chemotherapy for PSD has been the traditional approach, but is hampered by limited entry into the peritoneum. Any systemic chemotherapy for intraperitoneal disease must overcome the plasma-peritoneal partition to reach molecular targets. Pharmacokinetic studies have 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.31-33 Delivery of intraperitoneal chemotherapy can be viewed as a tool to overcome this drug resistance, as well the toxicity attendant to systemic administration. Because of this partition, drugs without lipophilic properties and high molecular weights have optimal characteristics for intraperitoneal application. The pharmacokinetic advantage of intraperitoneal perfusion is substantial and can be quantified by the area under the curve ratios of peritoneal fluid to plasma that favor retention of drug in the peritoneum.34-40

In addition to the pharmacokinetic advantage that intraperitoneal chemotherapy infusion (after maximal tumor debulking) offers, the addition of hyperthermia effects cell membranes, cytoskeletons, synthesis of macromolecules, and DNA repair mechanisms.41,42 Our institution and others have primarily used MMC. The synergy between MMC and hyperthermia occurs independent of the cell cycle, allowing for considerable tumoricidal activity with relatively brief exposures.43-45 Additionally, the hyperthermia ameliorates the hypothermia frequently encountered during long open operative procedures.

There is a paucity of data on the use of systemic therapy for PSD in general, and for appendiceal tumors, specifically the more common low-grade tumors. Therefore, the foundation of treatment for PSD of appendiceal malignancies remains aggressive CS followed by hyperthermic peritoneal perfusion. Removal of bulk disease is imperative, however, as even the most ambitious perfusion strategies penetrate a maximum 5 mm into peritoneal surfaces. Aggressive CS allows hyperthermic chemoperfusion to address the microscopic or small-volume residual. Consequently, the foundation of treatment of PSD for appendiceal disease remains aggressive CS followed by HIPEC.

Pathologic characteristics clearly impact the clinical outcomes of patients with PSD. For appendiceal tumors, patients with low-grade mucinous carcinoma peritonei (which is also described as disseminated peritoneal adenomucinosis or pseudomyxoma peritonei [PMP]) experience better clinical outcomes than those with higher grade nonmucinous appendiceal malignancies.47-54 We, and others, have previously shown that the survival rate in patients with high-grade lesions was significantly lower than for the low-grade PSD.8,16,17 This is not an unexpected finding based on the biological and molecular differences between low- and high-grade nonmucinous appendiceal tumors.6,17,49 We have recently described the genomics of appendiceal tumors and found them to be dramatically different from colorectal epithelial neoplasms.49 Such studies are important to determining the

![Figure 3. Overall survival by primary tumor site, differences significant (p < 0.0001).](image3)

![Figure 4. Overall survival by preoperative performance status, differences significant (p < 0.0001).](image4)
biologic underpinnings of PMP and seeking actionable targets for personalized therapies.

Appendiceal cancer with PMP has been considered the classic indication for HIPEC, as PMP rarely metastasizes beyond the peritoneal space and pelvis. Five-year survival rates after HIPEC for PMP range between 66% and 97%, and our experience is consistent with those results.50-53 Tumor histology is a major driver of prognosis for patients with PMP. The outcomes with the low-grade disease with PSD are considerably better than those of intermediate- or high-grade disease in the original description of the histologic subtypes of PMP.55 We believe that the behavior of PMP/appendiceal carcinoma is best described simply as low and high grade rather than a more cumbersome 3-tier classification.16,17 This clearly demonstrates the differences in tumor biology among these histologic subgroups of PMP, and is readily reproducible when reviewed by pathologists.

This study confirms our previous reports that patients with Eastern Cooperative Oncology Group performance scores of 2 to 3 had significantly poorer overall survival than those with scores of 0 or 1.8,18 This also highlights the importance of evaluating candidates for the procedure when they are medically fit to undergo such a large-scale intervention. Preoperative performance scores and quality of life indices clearly predict outcomes.56 Therefore, we select patients for HIPEC with Eastern Cooperative Oncology Group scores of 2 or better. Despite recent improvements in systemic therapy for colorectal cancer, treating patients with second-line therapy when their performance status declines can deprive candidates of the opportunity to be salvaged with CS and HIPEC. We suggest that if systemic chemotherapy will be used preoperatively, that it be limited to 3 to 6 cycles to avoid substantial decrements in performance status attendant to prolonged systemic chemotherapy.56

Patients undergoing complete CS before HIPEC had superior outcomes compared with those who underwent incomplete CS regardless of site of the primary lesion (Fig. 5). This finding confirms data from our institution and others that demonstrate a considerable survival advantage for patients undergoing R0/R1 resection compared with those with R2 resections.8,18,57,58 In a review of 506 patients, Glehen and colleagues analyzed the survival of patients with peritoneal surface malignancies from colorectal primary tumors undergoing incomplete CS followed by HIPEC, and found that this treatment paradigm resulted in limited long-term survival.48 Patients who are unable to undergo significant CS (R2a or better) at laparotomy can be spared the potential toxicity of HIPEC. Our rate of complete cytoreduction increased substantially over time, which likely results more from better patient selection than from improvements in surgical techniques.

Surgical resection remains the primary mode of therapy for colon and rectal cancer. Treatment options for patients with unresectable metastatic disease have improved substantially in the past few years. Patients with stage IV colorectal cancer treated with newer combinations of cytotoxic chemotherapy59 and/or biological agents,60 have resulted in an unprecedented median survival of approximately 20 months, although at considerable cost. However, such therapeutic combinations are not an optimal treatment strategy for all categories of stage IV disease. Patients with PSD from colorectal cancer treated with modern systemic therapy have poorer survival rates than those with metastases to other sites, with 5-year survival rates of 6.0% vs 4.1% with modern
chemotherapy. Patients undergoing CS and HIPEC had a 5-year survival rate of 17%, with those undergoing R0/1 resections being more than 4 times that. This finding is consistent with other high-volume centers. In addition, it must be kept in mind that most of the patients undergoing HIPEC for colorectal cancer have been treated with systemic chemotherapy before HIPEC. Therefore, they are well into the 12.7-month median survival found with systemic chemotherapy alone, and present a treatment lead time against any benefit of HIPEC vs systemic therapy.

This experience is supported by the randomized trial from the Netherlands that compared palliative surgery with chemotherapy with CS and HIPEC with the same systemic chemotherapy before HIPEC. Therefore, they are well into the 12.7-month median survival found with systemic chemotherapy alone, and present a treatment lead time against any benefit of HIPEC vs systemic therapy.

This experience is supported by the randomized trial from the Netherlands that compared palliative surgery with chemotherapy with CS and HIPEC with the same systemic chemotherapy. That randomized trial found a doubling of survival for patients treated with CS and HIPEC. Therefore, we concur with the consensus statement from the American Society of Peritoneal Surface Malignancies that systemic therapy alone is no longer appropriate for patients with limited peritoneal dissemination from a primary or recurrent colon cancer. The surgical management of PSD of colorectal origin with CS and HIPEC has been clearly defined and continues to improve. This aggressive strategy has resulted in long-term survival rates that are unprecedented in the literature. Despite the cost of considerable morbidity, properly selected patients have a real opportunity for survival in a situation that was previously approached with purely palliative intent.

We have avoided addressing PSD from hepatic, biliary, and pancreatic sources principally because of difficulty obtaining control of the primary lesion, and a paucity of agents with considerable activity. Similarly, we currently consider patients with gastric cancer after a response to systemic chemotherapy and only if R0/1 resection can be anticipated. Peritoneal surface (malignant) disease from sarcoma (sarcomatosis) is now a rare indication for HIPEC. Although we had some success with the procedure and have long-term survivors, we have no confidence in the activity of the chemotherapy in this setting, and no longer offer the procedure to patients with disseminated gastrointestinal stromal tumors or liposarcoma.

Primary peritoneal mesothelioma is a much less common entity than the pleural malignancy. Although the molecular characteristics of peritoneal disease differ only slightly from the pleural disease, the clinical courses are disparate. Peritoneal disease typically presents with ascites, abdominal pain, and eventually bowel obstruction. The disease tends to remain within the abdominal cavity until late in the course and distant metastasis is distinctly uncommon, making this an excellent opportunity for CS and HIPEC. We and others have previously reported our experience with this modality, which represents a great improvement over even the best systemic

### Table 3. Univariate and Multivariate Analysis of Prognostic Significance of Clinicopathologic Variables Based on Stepwise Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>p Value</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Peritoneal carcinomatosis index</td>
<td>&lt;0.0001</td>
<td>1.28 for each 5-unit increase</td>
</tr>
<tr>
<td>Resection status</td>
<td>&lt;0.0001</td>
<td>1.6—5.7</td>
</tr>
<tr>
<td>Sex</td>
<td>0.039</td>
<td>0.85</td>
</tr>
<tr>
<td>Complications</td>
<td>&lt;0.0001</td>
<td>1.5</td>
</tr>
<tr>
<td>Length of operation</td>
<td>0.041</td>
<td>1.03 (each additional hour)</td>
</tr>
<tr>
<td>Previous CS and HIPEC</td>
<td>&lt;0.0001</td>
<td>0.45</td>
</tr>
<tr>
<td>Age</td>
<td>0.028</td>
<td>1.04 (each 5-year increase)</td>
</tr>
<tr>
<td>Temperature of perfusate</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Length of perfusion with chemotherapy</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Primary tumor histology (site)</td>
<td>&lt;0.0001</td>
<td>0.24—2.7 (depending on primary)</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>&lt;0.0001</td>
<td>2.8 for 2, 4.3 for 3 or 4</td>
</tr>
<tr>
<td>Experience quintile</td>
<td>0.006</td>
<td>1.5 (quintile 1 vs 5)</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection status</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Primary tumor histology (site)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Complications</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Experience quintile</td>
<td>0.043</td>
<td></td>
</tr>
</tbody>
</table>

CS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy.
In our initial study, we used MMC as the agent but have changed to cisplatin after reports from the surgery branch of the National Cancer Institute. 

The experience with CS and HIPEC for peritoneal mesothelioma has led to a proposed staging system, which we support. We believe that mesothelioma represents one of the strongest cases for combining HIPEC with CS.

It is estimated that only a handful of patients who are potential candidates for CS and HIPEC actually receive it, which is underscored by the relatively small number of patients accrued to the trials and studies for PSD at large perfusion centers. It is clear that expanding the number of centers should be done 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. This has led to consensus statements by a group of surgeons with an interest in CS and HIPEC, which outlines an evaluation strategy for PSD from colorectal carcinoma.

Although results reported from perfusion centers represent a substantial improvement in duration and likely quality of life, the majority of patients undergoing these procedures will experience tumor recurrence. Evaluating patients for a second CS and HIPEC will become an ever more common problem as patients with PMP survive long enough to require multiple procedures.

We and others believe that, in selected patients, a second CS and chemoperfusion can be of value (Fig. 7). 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 enough to tolerate a major operative procedure, be free of extra-abdominal metastasis, 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 to proceed with another procedure. Patients with bulk residual disease after an initial cytoreduction for PSD should not be considered candidates for second cytoreductive procedures.

In this study, 89 patients underwent a second (or third) HIPEC. In this study, 89 patients underwent a second (or third) HIPEC. Although such cases had good outcomes, with survival similar to the experience with an initial procedure, when chosen appropriately iterative procedures can “reset the clock” to the time of the initial HIPEC. We do recognize that this survival advantage clearly represents a selection bias in choosing patients for repeat procedures.

Several issues surround the future of CS and HIPEC for PSD. Chief among them is how to make such therapy standardized and available to large numbers of patients. There are currently approximately 100 active centers in the United States, but only approximately a dozen with experience of >100 cases. These operative procedures require aggressive cytoreduction and are lengthy, challenging, potentially morbid, and use a great deal of hospital, blood bank, and surgical house officer resources. Resource use and safety of chemotherapy in the operating room remain daunting for many centers. Additionally, great care needs to be taken in selecting patients to undergo this procedure. The financial cost of these procedures can be considerable; even considering the potential feasibility of laparoscopic approaches to selected patients with PSD, the cost of these procedures will remain substantial. However, when viewed in the context of the skyrocketing costs for multi-agent chemotherapy, with increasing use of biologic agents costing in excess of $100,000, we maintain that HIPEC should be cost effective for appropriately selected patients.

Our experience has evolved and improved during the 2 decades of this study. This implies a learning curve, which we estimate to be in the range of 50 to 200 cases. Although we would like to think our surgical techniques have improved considerably over time, we believe that it is primarily better patient selection that accounts for the improved outcomes. In addition, even with our experience, for most primary site tumors the optimal time, dose, temperature, and chemotherapeutic agent for perfusion are not based on class I data. Therefore, additional investigation into these variables remains important.

Fundamental questions about HIPEC for PSD need to be addressed. Foremost among these is whether the addition of HIPEC after CS is of value. It seems obvious that the value of HIPEC should depend on the tumor being treated. The only completed randomized trial for CS and HIPEC evaluated patients with PSD from colorectal primary and appendiceal
lesions. That trial compared CS and HIPEC with standard systemic chemotherapy with standard systemic therapy (fluorouracil and leucovorin) and found the CS and HIPEC doubled the survival. However, to date, no study has compared CS with or without HIPEC. Clearly, it would be desirable to evaluate the value of HIPEC vs CS alone in a multicenter prospective randomized trial, and such a trial in France is now accruing patients. However, such a randomized controlled trial has proven difficult to complete and efforts have previously failed, as many patients presenting themselves for evaluation refuse to consider such a randomization. Efforts to bring CS and HIPEC to multicenter trials have not been embraced by the cooperative oncology groups to date. A recent study offered via the American College of Surgeons Oncology Group accrued a single patient (coincidentally from our site), before closure due to lack of accrual. However, such difficulties in performing randomized trials do not mean they should not be pursued.

**CONCLUSIONS**

The advancement of Centers of Excellence as well as the initiation of cooperative group trials will help to define the improved approaches for peritoneal spread for PSD. The future of CS and HIPEC for PSD lies in multicenter and randomized trials that not only investigate response and survival, but also standardization of techniques, quality of life, and integration with ever-improving systemic therapy. Our experience clearly shows that long-term survival is possible after a diagnosis of PSD, and that approaching such patients with therapeutic nihilism is no longer appropriate.

**Author Contributions**

Study conception and design: Levine, Loggie

Acquisition of data: Levine, Stewart, Shen, Loggie, Votanopoulos

Analysis and interpretation of data: Russell

Drafting of manuscript: Levine

Critical revision: Levine, Stewart, Shen, Loggie, Votanopoulos

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**REFERENCES**


Discussion

DR CHARLES STALEY (Atlanta, GA): Historically, carcinomatosis from disseminated cancer has been associated with a short survival, poor quality of life, and unsatisfactory response rates to systemic chemotherapy. The Wake Forest group has been at the forefront of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for the last 20 years. This presentation highlighted their experience with 1,000 patients, which demonstrated that the primary site histology, performance status, and completeness of resection are the most important prognostic factors for long-term survival.

Similar to other complex surgical oncology operations, cytoreductive surgery and HIPEC can be done with low mortality and acceptable morbidity in experienced centers. What percentage of those patients who looked to be resectable at preoperative imaging are explored and found to be unresectable? And is there any role of laparoscopy in sorting out these patients? Because performance status is important, are there any minimal nutritional parameters you used to make patient selection? Are there certain pathologic subtypes, like signet ring histology, that you’d not consider for cytoreductive surgery and HIPEC based on their poor tumor biology?

As a relative newcomer in this field, I am discouraged by the lack of standardization of these procedures, chemotherapy, drug selection, and lack of clinical trials, which certainly adds to the skepticism of some about this treatment approach. What simple steps can we take to start to turn this around? We certainly need to continue to educate our medical oncology colleagues about this procedure and to facilitate early referral of more treatable patients with low-volume disease instead of the usual chemorefractory bulky disease with reduced performance status.

DR FREDERICK GREENE (Charlotte, NC): Today we have heard a landmark paper presented by Dr Levine and his colleagues, who are indeed experts in the technique of cytoreductive surgery and HIPEC for peritoneal-based malignancy. They have used a prospective database to carefully evaluate these 1,000 patients, and have shown that at least in the hands of experts, increasing experience is directly related to overall survival and inversely related to significant complications. You have not mentioned the use of laparoscopy either as a preoperative staging tool or as a method of attaining cytoreduction. Could you please discuss the use of a laparoscope in your patient population?

You state that the average time for these procedures is just under 10 hours. In this economic era, how can we effectively plan for operating room time and justify the use of personnel in initiating a program of cytoreductive surgery and HIPEC?

Finally, we continue to report 30-day morbidity and mortality in our discussions of operative outcomes. Because many patients continue to remain hospitalized or sustain complications beyond 30 days, have you looked at 60-day outcomes and beyond to assess morbidity and mortality directly related to cytoreductive surgery and HIPEC?

DR LD BRITT (Norfolk, VA): Not to sound like one of the officials in the Hunger Games at Capital City, but how would you respond to the insurance company pundit who would say this sort of approach is not cost effective?

DR WILLIAM CHAPMAN (St Louis, MO): This is a great paper and, really opens a lot of eyes to considering this option in patients with peritoneal disease. What about when there is resectable metastatic disease in the liver, but also peritoneal disease? Would we be considering the combination of major hepatectomy with peritoneectomy? More recently, we have taken the view for colorectal liver metastases that if all gross disease can be resected, proceed with hepatectomy. However, I think most liver surgeons at most liver centers with any component of significant peritoneal disease do not proceed and instead declare the patient unresectable. So I would be curious about any data you have in that regard to clarify if we should be considering resection in this setting also?

DR EMMANUEL ZERVOS (Greenville, NC): You commented on chemotherapy before, but I wonder if you might comment on what impact adjuvant chemotherapy had on your observation of improved outcomes in the latter quintiles.

DR EDWARD A LEVINE: First, in terms of laparoscopy, does it have a role? Yes, of course it does. For patients particularly with low volumes of peritoneal surface disease, it is possible to stage them to see if you are likely to be able to achieve satisfactory cytoreduction. Further, select low volume cases can be done laparoscopically. However, the problem is that many of these patients have had several operations previously, which can make mobilization exceedingly difficult or frankly, not possible. So there is a role for laparoscopy, but unfortunately, its role is limited because many of these patients, particularly once they have significant peritoneal volume of disease, are not going to be candidates for a laparoscopic approach.

In terms of nutritional status, yes, absolutely we look closely at nutritional parameters. We want to see an albumin close to the normal range, certainly above 3 g/dL. I usually tell my residents who are coming through for the first time to ask themselves if they would perform a Whipple procedure on these patients? If the answer is no, then the answer is no. Although some patients can become candidates with preoperative nutritional support, those who cannot should not be offered the procedure.

Histology of the primary lesion is a key prognostic variable. Further, patients who have signet ring cells, though not a part of this manuscript and analysis, have a poorer prognosis than those who did not have the signet ring histology, particularly for colon and appendiceal tumors. Those patients can be long-term survivors. However, they are going to need a more complete cytoreduction than others. Leaving gross disease behind in those patients will not likely be associated with long-term survival.

For morbidity and mortality, I presented a 30-day mortality rate. I would agree that frequently, and this procedure is no exception, mortality does not end at 30 days for processes that are directly related to the procedure. Probably a more reasonable number is 120 days, which is a number we don’t usually use. At 6 months, the overall mortality might be closer to 6%. Mortality continues to increase slightly over the course of the first 2 to 3 months before it levels off. And their performance status, and we’ve looked at quality of life for these patients,
really does not level out for about 2 months. However, by 6 months, quality of life measures are back to or above baseline in most cases.

Parenchymal hepatic metastases, but not hepatic surface or capsular disease, were considered a contraindication to the procedure for the first decade of our experience. However, we have found that if you can get a complete cytoreduction in the liver and the peritoneum—the "and" here is crucial because you have to clear all the disease from both sites—the overall survival actually looks quite similar. Although 5-year survival is not quite as good as you would expect for liver disease alone, it remains impressive to us. We have taken the approach that if liver disease can be completely cleared with less than a lobectomy or a combination of resections and radiofrequency ablations, and a complete peritoneal cytoreduction, leaving no gross disease behind, it’s probably worth pursuing in some selected patients.

Dr Britt cuts to the heart of the matter—how do you defend the cost? This is an expensive operation, make no mistake about it. The average hospital stays are lengthy, the operating room time expensive, and the procedures associated with it are expensive. The thing you have to keep in mind is what will happen to these patients if they do not undergo this procedure. A very, very few of them will be long-term survivors. Additionally, you have to compare that with the cost of systemic chemotherapy, which, if you have colon cancer, you use an oxaliplatin-based regimen, a irinotecan-based regimen, bevacizumab followed up with biologic agents. You are looking at perhaps $200,000 over the course of 2 years. If you view it in that light in terms of the entire history of cost to the patient, this procedure becomes cost effective, if not a bargain.