Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy for Peritoneal Surface Malignancy: Experience with 501 Procedures

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BACKGROUND: Peritoneal dissemination of abdominal malignancy (PSD) has a clinical course marked by bowel obstruction and death. We have been using aggressive cytoreductive surgery with intraperitoneal hyperthermic chemotherapy (IPHC) to treat PSD. The purpose of this article was to review our experience with IPHC.

STUDY DESIGN: A prospective database of patients undergoing IPHC has been maintained since 1991. Patients were uniformly evaluated and treated. Demographics, performance status, resection status, primary site, and experience quartile were compared with outcomes. Univariate and multivariate analyses were performed.

RESULTS: A total of 460 patients underwent 501 IPHC procedures. Average age was 53.0 years, and 50.4% were women. The 30-day mortality rate was 4.8%, the complication rate was 43%, and median hospital stay was 9 days. Median followup was 55.4 months, median survival was 22.2 months, and 5-year survival rate was 27.8%. Factors correlating with improved survival were performance status ($p = 0.0001$), primary tumor ($p = 0.0001$), resection status ($p = 0.0001$), complications ($p = 0.002$), previous IPHC ($p = 0.006$), and experience quartile ($p = 0.031$). On multivariate analysis, primary tumor site, performance status, resection status, and development of complications ($p < 0.001$) predicted outcomes.

CONCLUSIONS: Our experience demonstrated that preoperative criteria for better outcomes include primary tumor site and performance status. Completeness of resection and development of postoperative complications are also crucial, and outcomes have improved over time. Cytoreductive surgery and IPHC represent substantial improvements in outcomes compared with historic series and best-available systemic therapy. Longterm survival is possible for selected patients who undergo the procedure. (J Am Coll Surg 2007;204:943–955. © 2007 by the American College of Surgeons)

Disseminated malignant peritoneal surface disease (PSD), or carcinomatosis, has traditionally and justifiably been approached with therapeutic nihilism. Patients typically progress to death from bowel obstruction in less than a year.[1] PSD results from intracavitary dissemination of tumor from a variety of primary 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 extraabdominal disease. So, a regional approach to selected patients with PSD is reasonable.

In the 1980s, aggressive treatments of peritoneal surface malignancies were explored in an attempt to benefit through multimodality techniques. Centers explored treatment options such as peritonectomy procedures,[2] IP injection of anticancer drug OK432,[3] intracavitary immunotherapy, photodynamic therapy,[4,5] IP hyperthermic chemotherapy (IPHC), and early postoperative IP chemotherapy.[6-8] Over the past decade, there has been ever increasing interest in such regional therapy for PSD. This

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Abbreviations and Acronyms

CS = cytoreductive surgery
GIST = gastrointestinal stromal tumor
IPHC = intraperitoneal hyperthermic chemotherapy
MMC = mitomycin C
OS = overall survival
PMP = pseudomyxoma peritonei
PSD = peritoneal surface malignant disease

has been additionally stimulated by publication of a prospective randomized trial for PSD from colorectal sources[9] and recent successes with IP chemotherapy for PSD from ovarian cancer.[10,11]

The optimal management of patients with PSD is a matter of intense debate. Systemic chemotherapy for PSD is limited, in part, to its limited entry into the peritoneum. Localization of tumor within the peritoneum without distant metastasis makes an aggressive regional approach attractive. Several groups have treated peritoneal surface extension of appendiceal tumors with debulking procedures.[12-14] But it is clear that these procedures are frequently unable to remove all microscopic tumors.

Our approach to selected patients with PSD has been to combine aggressive cytoreductive surgery (CS), with the goal of resecting all gross disease, with chemoperfusion to address microscopic residual tumor. A chemotherapy perfusion done at the same time as CS has several advantages. First, intracavitary chemotherapy achieves drug levels far greater than can be obtained with even the most aggressive systemic administration, which may overcome relative intrinsic drug resistance. Next, after CS, all peritoneal surfaces are exposed, allowing for better drug distribution (versus postoperative) as all adhesions are lysed. Additionally, the single intraoperative dose eliminates major compliance and tolerance issues encountered with postoperative administration of several cycles of treatment.[10,11,15] The rationale for hyperthermia is based on laboratory studies showing synergy with certain drugs.

We have previously reported our early experience[8] and subsets of patients treated with CS and IPHC for PSD from appendiceal,[16,17] colorectal,[18,19] gastric,[20] and small bowel[21] carcinomas and mesothelioma.[22] This article reviews our prospective database of patients undergoing CS and IPHC for PSD to evaluate our experiences with the first 501 procedures.

METHODS

Patients who underwent CS and IPHC for PSD at Wake Forest University School of Medicine Baptist Hospital between 1991 and 2006 were identified from a prospective database. This database and analysis has been approved by the Institutional Review Board at Wake Forest University. All patients were evaluated in the surgical oncology clinics preoperatively. Evaluations included, at a minimum, a complete history, examination, pathologic review, CT imaging, blood counts, and renal and liver functions. To be considered for CS and IPHC, patients needed to have normal organ function (serum creatinine < 2 mg/dL, alkaline phosphatase and serum aspartate transaminase or alanine transaminase less than 3 times the upper limit of normal, white blood cell count $\geq 4{,}000/mm^3$, and platelet count $\geq 100{,}000$ mm^3. Evaluation of preoperative CT imaging focused on the absence of extraabdominal metastasis, parenchymal hepatic metastasis (hepatic surface lesions allowed), bulky small bowel disease, multistation bowel obstruction, and ureteral or biliary obstruction. Tumors were categorized according to the primary site of origin. Before CS and IPHC, 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 ureteral stent placement at the start of the procedure to facilitate retroperitoneal dissection. Clinical data on all patients were recorded in a database and maintained by a dedicated data management unit.

Cytoreductive surgery

The goal of cytoreductive surgery was removal of all gross disease in all patients. CS consisted of the removal of gross tumor and involved organs, peritoneum, or tissue deemed technically feasible and safe for the patient. This included routine supracolic omentectomy in all patients when it had not been previously performed. Peritonectomy procedures were performed as indicated.[2] Any tumors adherent or invasive to vital structures that could not be removed were cytoreduced using the cavitational ultrasonic surgical aspirator (CUSA, Valleylab). The resection status of patients was judged after CS using the following classification: R0, complete removal of all visible tumor and negative cytologic findings or microscopic margins; R1, complete removal of all visible tumor and positive postperfusion cytologic 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, patients were passively cooled to a core temperature of approximately 34° C to 35° C by