Ann Surg Oncol (2012) 19:110–114
DOI 10.1245/s10434-011-1840-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

The Role of Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy (CRS/HIPEC) in Patients with High-Grade Appendiceal Carcinoma and Extensive Peritoneal Carcinomatosis

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ABSTRACT

Background. Patients with peritoneal mucinous carcinomatosis (PMCA) of appendiceal origin and extensive disease are commonly advised against CRS/HIPEC. We hypothesize that CRS/HIPEC is a beneficial treatment for this group.

Methods. Retrospective analysis of 134 patients with appendiceal cancer treated with CRS/HIPEC was performed from a prospective database. Extent of disease, measured by peritoneal cancer index (PCI), was related to completeness of cytoreduction (CC), lymph node (LN) status, and prior surgery score (PSS). Overall survival (OS) was estimated by Kaplan-Meier curves. Test differences were calculated using log-rank test.

Results. A total of 77 patients (57%) had PMCA. Mean follow-up was 22 months with a median of 18 months. OS was 88%, 56%, and 40% for 1, 3, and 5 years, respectively. 68% had PCI $\geq$ 20. LN metastasis was found in 44% of patients in PCI $\geq$ 20 and PCI $<$ 20 groups. 73% and 60% of patients had PSS of 2 or 3 in PCI $\geq$ 20 and PCI $<$ 20 groups, respectively ($P = .196$). Complete cytoreduction was achieved in 65% of PCI $\geq$ 20 group and 96% of PCI $<$ 20 group ($P = .004$). With complete cytoreduction, the 5-year OS was 45% in PCI $\geq$ 20 group and 66% in PCI $<$ 20 group ($P = .139$). 18 of 19 patients with incomplete cytoreduction had PCI $\geq$ 20, with 3- and 5-year OS of 27% and 0%. Hazard ratios (by Cox regression) were 2.8 (95% confidence interval [95% CI] 0.8–10.2) and 3.6 (95% CI 1.5–8.8) for PCI $<$ 20 and complete cytoreduction, respectively.

Conclusions. Meaningful long-term survival could be achieved in patients with PMCA even with extensive peritoneal disease. PCI $\geq$ 20 should not be used as an exclusion criterion when selecting these patients for CRS/HIPEC, and every effort should be made to achieve complete cytoreduction.

Patients with extensive peritoneal dissemination from high-grade adenocarcinoma of the appendix represent a challenging group of patients to treat. Multiple phase II studies have suggested the effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for prolonging survival in patients with peritoneal dissemination from appendix cancer.[1–5] Some centers with expertise in peritoneal surface malignancy consider high-grade extensive disease a relative contraindication to CRS/HIPEC. However, the value of this approach in high-grade and extensive disease has not been well studied.

Several prognostic factors have been reported to impact outcome after CRS/HIPEC in appendix cancer. Peritoneal cancer index (PCI), completeness of cytoreduction (CC), prior surgery and histopathology have all been shown to affect survival.[1,2,4,6,7] Patients with high PCI scores are challenging surgically because of large-volume disease. PCI greater than 20 has been shown to be an adverse prognostic factor in multiple studies.[4,8]

Based on our experience with treating these challenging patients, we recommend CRS/HIPEC if preoperative evaluation suggests a high probability of complete cytoreduction. This study evaluates the outcome of patients with high-grade appendix cancer and extensive peritoneal carcinomatosis. We hypothesize that CRS/HIPEC is a

First Received: 2 March 2011;
Published Online: 24 June 2011

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beneficial treatment for this high recurrence risk group if complete cytoreduction can be achieved.

METHODS

Patients with appendiceal cancer and peritoneal spread who underwent CRS/HIPEC between years 1999 and 2010 were identified from a prospectively collected database. Informed consent was obtained preoperatively. High-grade disease was defined as peritoneal mucinous carcinomatosis (PMCA) per Ronnett's classification, and extensive disease was defined as PCI $\geq$ 20.[7,9] CT scan of the chest, abdomen, and pelvis and tumor markers (CEA, CA19-9, and CA 125) were obtained prior to surgery. After review of the CT scan and the patient's functional status (ECOG = 0, 1, or 2), surgery was recommended if complete cytoreduction was deemed feasible. Prior surgery score (PSS) was assessed as previously described by Jacquet et al.[10] Lymph node (LN) status was obtained from patients' previous surgeries and at the time of CRS/HIPEC. A single surgeon performed all operations. Of the 134 patients with appendiceal cancer and peritoneal spread, 57 patients with disseminated peritoneal adenomucinosis (DPAM) were excluded. The 77 patients with PMCA who underwent their first CRS/HIPEC at our institution were included and divided into 2 groups, PCI $\geq$ 20 and PCI $<$ 20, for comparison. Of the 77 patients, 20 had signet ring cells on pathology, and 2 of 77 had goblet cell carcinoma.

Under general anesthesia, a xypho-pubic incision was made. Disease extent was assessed, at the beginning and after CRS, by calculating PCI score as previously described by Jacquet et al. (Fig. 1).[10] Resections were done as needed to achieve complete cytoreduction, including excision of previous scar and port sites, anterior abdominal wall peritonectomy, splenectomy, cholecystectomy, greater and lesser omentectomy, diaphragmatic and pelvic peritonectomies, stripping of peritoneum over omental bursa and porta hepaticus, and visceral peritonectomies. Bowel and solid organs were removed, if disease could not be cleared. Every attempt was made to avoid stomas and extensive small bowel resections to help preserve quality of life. Extensive involvement of the small bowel not amenable to destruction or segmental resections in order to preserve adequate length did lead to incomplete cytoreduction in most cases.

Complete cytoreduction (CC) was defined as no visible tumor nodules or nodules less than 2.5 mm in size, using the CC score adopted by the consensus panel recommendations on peritoneal surface malignancies.[11] Following CRS, HIPEC was performed using a closed technique for 90 min before performing any anastomoses. Mitomycin-C was used with a dose of 40 mg; 30 mg given at time zero and 10 mg given 30 min later. The target outflow temperature was maintained at 41–42°C, which requires an inflow temperature of 42–43°C. Urine output was maintained between 250 and 400 cc/h during perfusion to avoid renal toxicity.

Patients were maintained in the intensive care unit during the first 24 hours of the postoperative period or until stable, and then transferred to the surgical floor. Early mobilization was encouraged, with physical therapy assistance on postoperative day 1. Low molecular weight heparin, compression stockings, and early mobilization were used for deep vein thrombosis prophylaxis. Patients were discharged when clinically stable; low molecular weight heparin was continued on an outpatient basis for 21 days.

Follow-up for all patients was carried out at 3 weeks, 3 months, and every 6 months thereafter. CEA, CA19-9, and CA 125 tests with CT scans of the chest, abdomen, and pelvis were performed 1-month postoperatively, at 6-month intervals for 5 years, and yearly thereafter. The disease recurrence/progression was determined on clinical grounds based on the physical exam and test and scan data. No patients were lost to follow-up.

Data was collected prospectively at patients' follow-up visits. Comparisons between groups (PCI $\geq$ 20 vs PCI $<$ 20) were performed using the chi-square test for categorical variables and variance analysis for continuous variables. Overall survival (OS) was calculated from the date of CRS/HIPEC to the date of death. Estimates of survival were calculated using the Kaplan-Meier method. Differences were calculated with a log-rank test. Cox proportional hazard ratio was used to compare pertinent variables. Cox proportion hazard regression model was used to perform multivariate regression analysis. Results were considered statistically significant if $P < .05$. The institutional review board approved this study.

RESULTS

A total of 77 patients with PMCA were entered into the study. The female-to-male ratio was 44:33. The mean age at diagnosis was 50 years, with a range of 26–74 years. Mean age at surgery was 52 years, with a range of 28–79 years. Mean time from diagnosis to first CRS/HIPEC was 25 months for PCI $\geq$ 20 vs 9 months for PCI $<$ 20 ($P = .04$).

Overall, 52 patients (68%) had a PCI $\geq$ 20; 53 patients (69%) had a PSS of 2 or 3; 34 patients (44%) had LN metastasis. Complete cytoreduction was achieved in 58

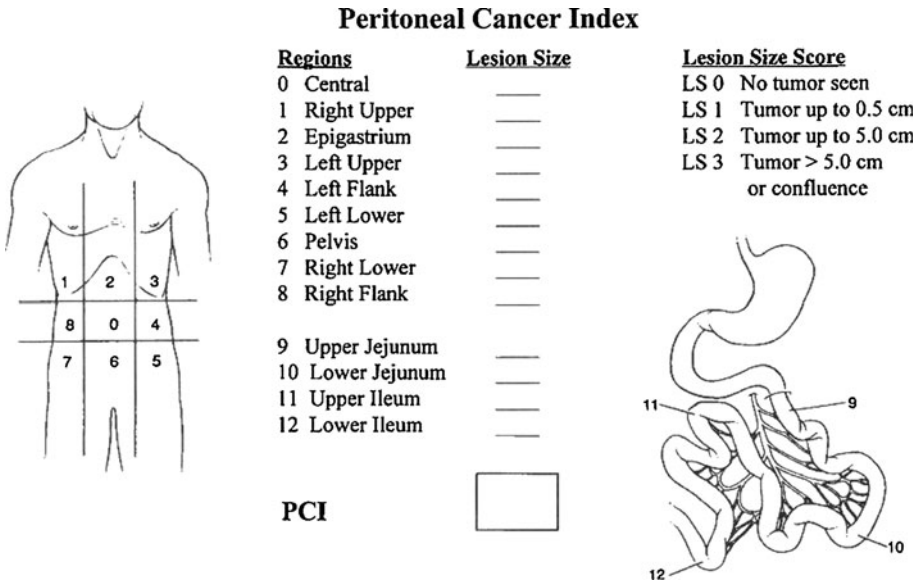

FIG. 1 Peritoneal Cancer Index score (with permission from Sugarbaker et al.)

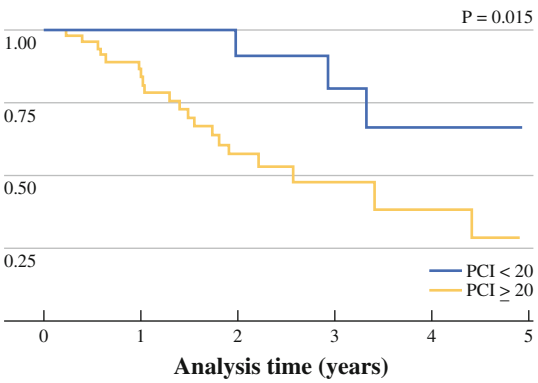

FIG. 2 Overall survival by Peritoneal Cancer Index

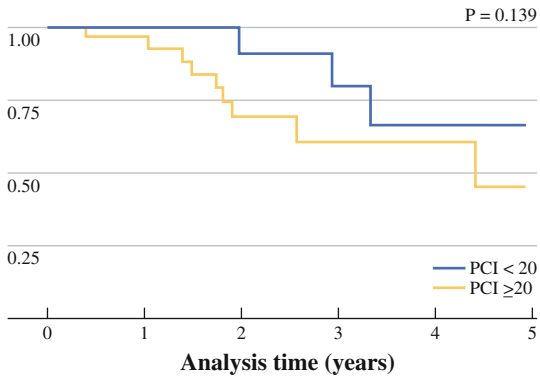

FIG. 3 Overall survival by Peritoneal Cancer Index in patients with complete cytoreduction (CC 0 or 1)

patients (75%). In the PCI $\geq$ 20 group, 23 patients (44%) had LN metastasis; in PCI $<$ 20 group, 11 patients (44%) had LN metastasis ($P = .985$). In the PCI $\geq$ 20 group, 38 patients (73%) had a PSS of 2 or 3; in the PCI $<$ 20 group, 15 patients (60%) had a PSS of 2 or 3 ($P = .196$). Complete cytoreduction was achieved in 65% of the PCI $\geq$ 20 group and 96 % of the PCI $<$ 20 group ($P = .004$).

At a mean follow-up of 22 months and median follow-up of 18 months (range 3–90 months), 53 patients (69% of 77) were alive and 24 patients (31% of 77) were deceased as of January 2011. Of the deceased, 22 (29% of 77) died of disease and 2 from other causes. Of the 53, 37 (48% of 77) were alive with no evidence of disease. Also, 16 of 53 (21% of 77) were alive with disease. The median survival was 3.4 years. Calculated OS was 88%, 56%, and 40% for 1, 3, and 5 years, respectively. The 5-year OS was 76% for LN negative status and 11% for LN positive patients ($P < .001$). Five-year OS was 48% for patients with PSS of 0 or 1 and 52% for patients with PSS of 2 or 3 ($P = .895$). The 5-year OS was 52% for patients with complete cytoreduction and 0% for patients with incomplete cytoreduction ($P < .001$). The 5-year OS was 29% for patients in the PCI $\geq$ 20 group and 66% for patients in the PCI $<$ 20 group ($P < .015$) (Fig. 2). The 5-year OS was 45% for patients in the PCI $\geq$ 20 group and 66% for patients in the PCI $<$ 20 group when complete cytoreduction was achieved ($P = .139$) (Fig. 3). There were 19 patients who had incomplete cytoreduction. Of the 19, 18 had a PCI $\geq$ 20, with 3-year OS of 29%, and no one alive at 5 years. On multivariate analysis, using Cox regression with PCI $\geq$ 20 and incomplete cytoreduction, hazard ratios were 2.8 (95% confidence interval [95% CI] 0.8–10.2) and 3.6 (95% CI 1.5–8.8), respectively.

The 30-day postoperative and in-hospital mortality were zero. Major postoperative complications included pancreatic leak in 8 patients (10.4%), anastomotic leak that developed a fistula in 1 patient (1.3%), pneumonia in 10 patients (13%), and acute renal failure in 2 patients (2.6%).

DISCUSSION

This study was performed on a distinct cohort of patients with high-grade and extensive peritoneal disease. PMCA histopatholgy has been shown to have adverse prognostic effect on long-term survival.[5,6,12] PCI score has also been shown to be an adverse prognostic factor. Elias et al. in a multicenter study of 301 patients, reported that PCI > 19 is an independent prognostic factor.[13] Our results concur that extensive disease in patients with PMCA is an adverse prognostic factor. However, the fact that PCI score lost its statistical significance once we controlled for CC suggests that extensive disease should not be an exclusionary criterion for surgery even in high-grade disease. Instead, complete cytoreduction of extensive disease is a more important factor, and all efforts should be made at surgery to achieve CC, keeping in mind quality of life after surgery. However, that requires longer operative time and advanced surgical expertise in treating such disease.

Patients with extensive disease (PCI ≥ 20) had an average of 25 months between diagnosis and CRS/HIPEC, compared with only 9 months in patients with PCI < 20 ($P = .04$). In our experience, most of that time was spent receiving systemic chemotherapy on a palliative basis using advanced colon cancer regimens. However, there are very few reports about the efficacy of systemic chemotherapy in the treatment of appendix cancer.[14]We believe that this approach is delaying surgical intervention and leading to progression of disease, thus hindering the efforts for CC, a known independent prognostic factor.[1,2,4,9] In this study, we showed that patients with PCI < 20 have a statistically significant higher chance of CC (96%), than patients with PCI ≥ 20 (65%) ($P = .004$). Of 19 patients with incomplete CRS, 18 had a PCI ≥ 20 and none of these patients was alive at 5 years. We propose that systemic chemotherapy could play a role in a subset of patients as a bridge to CRS/HIPEC, when used for a short duration, but patients should be evaluated first by a multidisciplinary team with expertise in peritoneal surface malignancy.

An aggressive surgical approach has been successful in treating liver metastasis from colorectal primary, and it is now the standard of care, based primarily on phase II data. As for peritoneal spread from appendix cancer, some advocate a palliative approach.[15] Miner et al. reported 21% (20 of 97) 10-year survival after serial debulking procedures. Among 10-year survivors, only 2 patients had high-grade disease; recurrence rate was 91%. Low-grade disease and CC were associated with prolonged survival on multivariate analysis; extent of disease was not described.[16] Sugarbaker reported 45% 20-year survival among patients with PMCA after CRS/HIPEC.[8] Our results support the fact that CC is essential for long-term survival as shown by Miner et al. and Sugarbaker. Longer survival data in our study and that of Sugarbaker's could be attributed to an aggressive surgical approach and the addition of HIPEC to the treatment regimen. One randomized trial has been published showing prolongation of survival in patients with peritoneal carcinomatosis of colorectal origin treated with CRS/HIPEC.[17,18] We believe conducting a multicenter randomized trial to address the effectiveness of regional therapy (HIPEC) would be ideal. However, the feasibility of such a study is questionable, given that multiple reports already suggest that CRS/HIPEC is effective, other effective treatments have not been identified, and the belief among experts on appendiceal cancer that CRS/HIPEC should be the standard of care, based on several positive phase II trials.[4,5,8,12,13]

Selecting patients for CRS/HIPEC remains challenging. Reviewing previous reports to establish guidelines for the selection is difficult partly because of the lack of consensus about pathology. Ronnett's classification is the most widely used, but different classification systems have been suggested.[19,20] In addition, extent of disease is not reported in all studies. At our institution, we do not consider grade or extent of disease a contraindication to CRS/HIPEC. We make every effort to achieve CC, while minimizing visceral resection and preserving quality of life after surgery. These decisions are usually made intraoperatively. A 65% CC and 45% 5-year OS for the high-risk group in our study support the strategy for aggressive surgical intervention. However, efforts for standardization of pathological reports are essential for future research and advancement in the treatment of this disease and direct the focus of our future projects.

This study is a retrospective analysis with inherent limitations and relatively short mean follow-up. However, we did not deselect patients based solely on pathology type and tumor burden, and we closely monitor our patients postoperatively. To our knowledge, this study is the first to specifically study PMCA patients with extensive disease. We can conclude that delaying CRS/HIPEC may complicate the surgical approach and lower the possibility of CC, which is documented in several studies to be essential for long-term survival. Meaningful long-term survival can be achieved in patients with PMCA even with extensive peritoneal disease. A PCI ≥ 20 should not be used as an exclusion criterion when selecting patients with high-grade disease for CRS/HIPEC, and every effort should be made to achieve complete cytoreduction.

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