Complete Cytoreduction Offers Longterm Survival in Patients with Peritoneal Carcinomatosis from Appendiceal Tumors of Unfavorable Histology

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BACKGROUND: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a rapidly evolving treatment for metastatic appendiceal neoplasms. The aim of this study was to show the effect of complete cytoreduction (CC) on survival in patients undergoing CRS and HIPEC for high-grade appendiceal neoplasm.

STUDY DESIGN: A retrospective study of a prospective database of 56 patients (from 1999 to 2007) with appendiceal neoplasms treated with CRS and HIPEC was carried out. Histology of the disease, CC score, and peritoneal cancer index (PCI) score were assessed independently and collectively for each group of patients. Survival analysis was performed using the Cox proportional hazard model.

RESULTS: Three-year overall survival was 60%. The median peritoneal cancer index score was 25 or higher. Survival analysis by tumor histology was 80% for patients with low-grade tumors and 52% for patients with high-grade tumors ($p = 0.024$). Survival by completeness of cytoreduction was 78% for patients with a low CC score (0 to 1) and 28% in patients with a high CC score (2 to 3; $p = 0.01$). There was no statistically significant difference in survival between the low-grade and high-grade tumors when a complete cytoreduction was performed in both groups of patients: 80% versus 68% ($p = 0.69$).

CONCLUSIONS: CRS and HIPEC is an effective treatment for patients with disseminated appendiceal tumors. High-grade tumors also benefit from this approach and should not be excluded from CRS and HIPEC. Every effort should be made to achieve a complete cytoreduction regardless of the tumor histology. (J Am Coll Surg 2009;209:308–312. © 2009 by the American College of Surgeons)

Appendiceal neoplasms are rare tumors and it is difficult to diagnose the extent of disease before operation. They often present as a ruptured appendix with peritoneal dissemination of tumor cells. This can progress to mucinous ascites, giving rise to the so called "jelly belly" with compression of the abdominal viscera. The clinical course of the disease depends on the histology of the tumor.[1]

The low-grade tumors usually have a slow clinical course and longer survival. On the contrary, high-grade tumors such as adenocarcinoids, goblet cell, and tumors with signet ring cells show a more aggressive clinical course compared with the low-grade variant. Multiple studies have demonstrated that cytoreductive surgery (CRS) adenomucinosis and hyperthermic intraperitoneal carcinomatosis chemotherapy (HIPEC) is an effective treatment for low-grade appendiceal tumors.[2-4] Traditionally, patients with more aggressive appendiceal tumors are considered poor candidates for CRS and HIPEC.[5]

Previous studies have shown that a high peritoneal cancer index (PCI) score associated with aggressive tumors (peritoneal mucinous [PMCA]) relates to increased difficulty in performing a complete cytoreduction.[5] In addition, it has been suggested that a PCI higher than 20 has

Disclosure Information: Nothing to disclose.

Presented at the American College of Surgeons 94th Annual Clinical Congress, San Francisco, CA, October 2008.

Received February 26, 2009; Revised March 31, 2009; Accepted April 14, 2009.

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ISSN 1072-7515/09/$36.00
doi:10.1016/j.jamcollsurg.2009.04.019

Abbreviations and Acronyms

CC = completeness of cytoreduction
CRS = cytoreductive surgery
DPAM = disseminated peritoneal
HIPEC = hyperthermic intraperitoneal carcinomatosis chemotherapy
PCI = peritoneal cancer index
PMCA = peritoneal mucinous

been considered a contraindication for CRS and HIPEC in patients presenting with these aggressive tumors.[6] This study shows the impact of complete cytoreduction on survival in patients with high-grade tumors and high PCI score. Our hypothesis is that in appropriately selected patients with high-grade appendiceal cancers, completeness of cytoreduction (CC) predicts longterm survival better than tumor histology.

METHODS

A retrospective study of a prospective database (1999 to 2007) was carried out on 56 patients with appendiceal cancer who underwent CRS and HIPEC. No patients were lost to followup. Informed consent was obtained preoperatively. Patients had no evidence of extraabdominal metastases and all had an Eastern Cooperative Oncology Group (ECOG) performance status sufficient to undergo major surgery. Patients were staged with CT scan of the chest, abdomen, and pelvis. Tumor markers (CEA, CA 19-9, and CA 125) were drawn the day before surgery.

Under general anesthesia, a midline xiphopubic incision was used to gain access to the abdominal cavity. Tumor burden was calculated using the PCI as reported by Sugarbaker.[7] Lesion size score was applied to each of the nine abdominopelvic regions, the jejunum, and the ileum. Summation of the lesion size score gives the PCI (range 1 to 39). Surgical resection of the primary tumor was done followed by peritonectomy procedures originally described by Sugarbaker.[7] The extent of operation was determined by the size and location of the tumor. The objective was to remove all visible tumor (complete cytoreduction).

Peritonectomy procedures were done as needed to achieve a good cytoreduction. These included anterior abdominal wall peritonectomy; greater omentectomy and splenectomy; left and right upper quadrant peritonectomies with stripping of the respective hemidiaphragms, which required placement of chest tubes; lesser omentectomy with cholecystectomy and striping of the omental bursa and porta hepatis; pelvic peritonectomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without anterior resection of the rectum.

Table 1. Surgical Resections in 56 Hyperthermic Intraperitoneal Carcinomatosis Chemotherapy Patients

Procedures	n
Partial gastrectomy	7
Small bowel resection	28
Right hemicolectomy	20
Left hemicolectomy	20
Resection of recurrence at previous anastomosis	6
Splenectomy	26
Total abdominal hysterectomy	8
Bilateral salpingo-oophorectomy	8
Right upper quadrant peritonectomy	42
Left upper quadrant peritonectomy	40
Pelvic peritonectomy	13
Partial pancreatectomy	7
Cholecystectomy	31
Omentectomy	43
Total colectomy	5

Visceral peritonectomy and resection were also needed to accomplish this goal. Every attempt was made to preserve as much bowel as possible and to avoid ostomies, taking into consideration the patient's quality of life after the procedure. Final assessment of cytoreduction was recorded based on the CC score. A complete cytoreduction (CC 0 to 1) denotes a tumor size of ≤ 0.25; an incomplete cytoreduction (CC 2 to 3), denotes a tumor size > 0.25 cm. Resected specimens were sent for pathologic evaluation to determine the type of tumor and degree of differentiation. A list of surgical resections carried out on the 56 patients is displayed in Table 1.

After the cytoreduction and before any anastomoses were made, HIPEC was performed intraoperatively with mitomycin C for 90 minutes at a total dose of 40 mg (30 mg given initially and 10 mg added after 30 minutes of perfusion) using a closed technique. The outflow temperature was maintained at 41° to 42°C. Urine output was maintained at 250 to 400 mL/h by using crystalloids and albumin to prevent renal toxicity. On completion of perfusion, the abdomen was reopened and gastrointestinal reconstruction was done as appropriate.

The patients were transferred to the ICU and subsequently to the surgical floor when stable. Physical therapy was started on postoperative day 1 and early mobilization was encouraged. Deep vein thrombosis prophylaxis was implemented using compression stockings, low molecular weight heparin, and early mobilization. Patients were discharged from the hospital when clinically stable. Clinical followup was done every 3 months for the first 2 years and every 6 months thereafter. Followup included complete clinical examination, tumor marker levels (CEA, CA19.9, CA125) done every 3 months, and CT scan of chest, ab-

Table 2. Grouping Patients by a Combination of Tumor Histology and Completeness of Cytoreduction Score, Showing Survival and Median Peritoneal Cancer Score in Each Group

Histology/CC score	Alive, n	Dead, n	Total, n	Median PCI/range
Low-grade tumor (DPAM) with CC score of 0/1	16	2	18	30 (4–37)
Low-grade tumor (DPAM) with CC score of 2/3	4	0	4	38 (36–39)
High-grade tumor (PMCA) with CC score of 0/1	19	4	23	25 (1–39)
High-grade tumor (PMCA) with CC score of 2/3	3	8	11	36 (25–39)
Total	42	14	56	

CC, completeness of cytoreduction; DPAM, disseminated peritoneal; PCI, peritoneal cancer index; PMCA, peritoneal mucinous.

domen, and pelvis done every 6 months for 5 years and yearly thereafter.

Peritoneal tumors were classified as described by Ronnet and colleagues[1] into two categories: low-grade or disseminated peritoneal (DPAM) and high-grade or PMCA. Tumors with discordant features, signet ring cell, goblet cell, and adenocarcinoids were grouped with the high-grade tumors. Standard life-tables were used to calculate 1-, 2-, and 3-year survivals (95% confidence intervals are reported). Followup times were administratively censored at 3 years because only 12 of the patients (22%) had more than 3 years of followup.

Chi-square test was used to test for associations between categorical variables. Ordinary least squares regression and logistic regression were used to model continuous and discrete variables as appropriate. Cox proportional-hazards models were used to test the influence of different variables on survival. The models were adjusted for age at operation and gender. The software used was STATA version 9.0.

RESULTS

Fifty-six patients were included in the study. The male: female ratio was 26:30; mean age was 52 years (range 30 to 80 years). There was no perioperative mortality and there were no anastomotic leaks. Two reoperations were required for bleeding. Mean length of hospital stay was 12 days. Twenty-two patients (39.2%) had low-grade tumors, and 34 patients (60.7%) had high-grade tumors. Median followup was 23 months (range 2 to 83 months). Fourteen patients died during followup. In all groups the median PCI was 25 or higher and complete cytoreduction was achieved in 41 patients (73%; Table 2). The 3-year survivals for all patients who had complete cytoreduction (CC 0/1) versus those who had incomplete cytoreduction (CC 2/3) were 78% and 28%, respectively, ($p = 0.01$; hazard ratio 5.6; 95% CI, 1.8 to 17.20; Fig. 1).

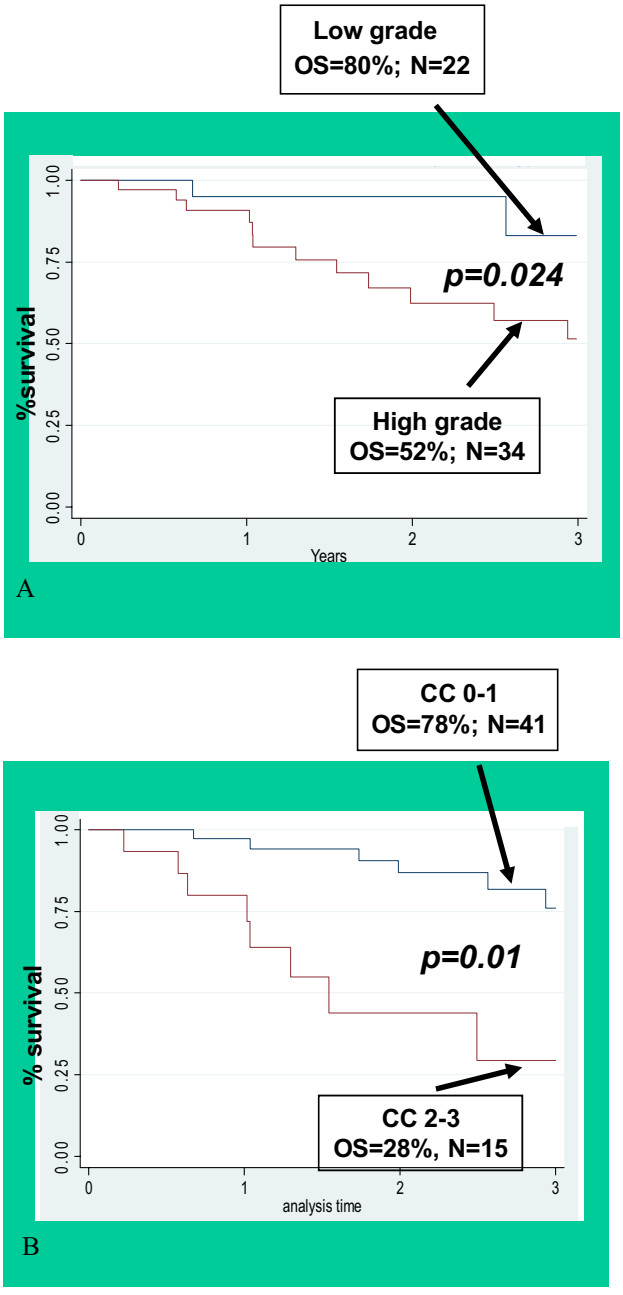

Figure 1. Kaplan Meier curves each showing 3-year survival of patients by (A) tumor histology and (B) completeness of cytoreduction. HR, 5.6 (95% CI, 1.8 to 17.20). CC, completeness of cytoreduction; OS, overall survival.

Patients with low-grade tumors had a statistically significant higher 3-year survival than patients with high-grade tumors (80% versus 52%, respectively; $p = 0.024$). There was no statistically significant difference in survival at 3 years in patients with low-grade tumors versus patients with high-grade tumors if complete cytoreduction was performed in both groups (80% versus 68%; $p = 0.69$; Fig. 2).

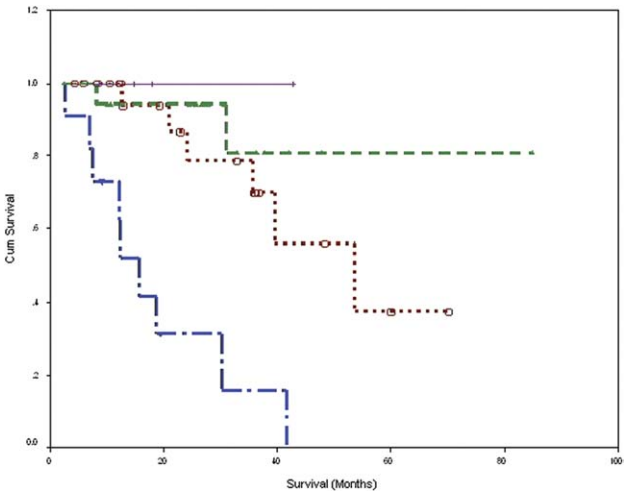

Figure 2. Kaplan Meier curves showing survival (OS) of patients according to a combination of tumor histology and the completeness of cytoreduction (CC). Blue dashed line, high-grade (CC, 2–3; OS, 9%; n, 3/11); red dotted line, high-grade (CC, 0–1, OS, 68%, n, 19/23); green dashed line, low-grade (CC, 0–1, OS, 80%, n, 16/18); purple line, low-grade (CC, 2–3, OS, 100%, n, 4/4).

Those with low-grade tumors and CC scores of 0/1 versus CC scores of 2/3 had survivals of 80% and 100%, respectively. But this test lacks power because of the small number of patients in the low-grade tumor group with a high CC score. Patients with high-grade tumors and CC score of 0/1 versus a CC score of 2/3 had survivals of 68% (n = 23) and 9% (n = 11), respectively (p = 0.264).

DISCUSSION

Several histopathologic descriptions of appendiceal neoplasms have been proposed with no consensus reached as to standard. In this study, we used the description put forward by Ronnet and associates[1] to categorize our patients. DPAM (low-grade) tumors appeared more histologically benign. They produce large amounts of mucin, rarely invade organs, and do not usually have lymphatic metastases. They are usually confined to the abdominal cavity, as a result, and may have been present for a considerable length of time at the time of diagnosis. PMCA (high-grade) tumors, on the other hand, are histologically more aggressive and are characterized by a more differentiated pattern of histology, including signet ring cells, which denote a more aggressive process with metastatic potential. Some studies have shown that patients diagnosed with the more aggressive form of the disease should be excluded from having CRS and HIPEC as a treatment option if there is extensive spread of the disease in the abdominal cavity.[5] Others have reported that a PCI ≤ 20 and the possibility of a complete cytoreduction would be required for an elective intervention.[6] In this study, a median PCI of ≥ 25 was present in all groups of patients, so most patients had extensive tumor involvement of the abdominal cavity. In spite of this, a low CC score was achieved in 73% of the total patient population. Sixty-eight percent of patients with PMCA and 82% of those with DPAM had complete cytoreduction.

Patients with a high PCI score usually present with massive disease, with involvement of the stomach, bowel, porta hepatis, and widespread pelvic and peritoneal disease that requires a more technically demanding procedure. This results in a longer operating time with the possibility of complications. Interestingly, we were able to perform a good cytoreduction with no mortality, no anastomotic leaks, and with a relatively short hospital stay.

This procedure can be performed with acceptable morbidity and mortality through accumulated experience.[8] Multiple studies from different centers have repeatedly demonstrated the impact of tumor biology on survival in patients with peritoneal carcinomatosis.[1,6] Patients with the more aggressive histologic variant (PMCA) usually have a worse survival outcome compared with the histologically more benign type. Data from this study have corroborated such findings (Fig. 1). It can also be seen from this study that in patients with a high-grade tumor having a high PCI score, an aggressive attempt to attain a low CC score was beneficial.

Survival at 3 years between the low-grade and the high-grade tumor groups was not statistically significant (p = 0.69) when a complete cytoreduction was performed in both groups of patients (80% versus 68%, respectively; Fig. 2). If a complete cytoreduction was not performed, the 3-year survival was only 9% for patients with high-grade histology. This finding demonstrates that it is possible to achieve the same survival outcomes with low- and high-grade lesions when a complete cytoreduction is performed. A similar observation has been reported by Elias and coworkers[2] in regard to the importance of complete cytoreduction with respect to tumor biology. There is a wide margin in survival in patients with high-grade tumors that are completely reduced compared with those that are not completely reduced (68% versus 9%). But this was not statistically significant (p = 0.264). A possible explanation for this p value is that the patient population size in this study group was small.

The overall 3-year survival was 60% in patients with appendiceal neoplasms, which is comparable with results from recent studies done within the last 5 years in other centers (Table 3). Of note, a greater percentage of patients in our study population had high-grade tumors when compared with patients in other studies in which high-grade tumors accounted for only ≤ 50% of the total group. In

Table 3. Comparison of Multicenter Survival Statistics of Patients with Peritoneal Carcinomatosis

		Histology, % of total patient population				Overall survival, %		
		DPAM		PMCA				Mean PCI score
First author, year	n	n	%	n	%	3y	5y	
Stewart IV[9] 2005	110	55	50	55*	50	59	53	—
Smeenk[3] 2007	103	66	64†	36*	35†	71	60	—
Baratti[10] 2008	95	78	74	26	26	n/a	72	21
Elias[11] 2003	36	22	61	14*	39	n/a	66	21
This study	56	22	39	34	61	60		25

*Including patients with PMCA and PMCA-1 as a group.
†Data missing in one patient.
DPAM, disseminated peritoneal; PCI, peritoneal cancer index; PMCA, peritoneal mucinous.

addition, their PCI scores were not as high as those in our study. Our 3-year followup time is relatively short compared with those in other studies. For high-grade tumors, it is a reasonable time for followup because these tumors' natural history has a high mortality rate within this time frame.

In conclusion, CRS and HIPEC is an effective treatment for patients with DPAM tumors. High-grade tumors also benefit from this approach and should not be excluded from this treatment modality. Every effort should be made to accomplish a complete cytoreduction regardless of the tumor histology. Because our patient followup time was relatively short and our patient population was small, more study is necessary to validate the survival benefit for patients with PMCA tumors in whom a low CC score can be achieved.

Author Contributions

Study conception and design: Omohwo, Nieroda, Studeman, Gushchin, Sardi
Acquisition of data: Omohwo, Studeman, Thieme, Kostuik, Holter, Sardi
Analysis and interpretation of data: Omohwo, Nieroda, Gushchin, Merriman, Sardi
Drafting of manuscript: Omohwo, Nieroda, Sardi
Critical revision: Omohwo, Nieroda, Thieme, Gushchin, Sardi

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