Delay of Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy in Patients with Appendiceal Neoplasm

HATEM EL HALABI, M.D., RYAN MACDONALD, PH.D., KIMBERLY STUDEMAN, M.D., JENNIFER FRANCIS, CAROL NIERODA, M.D., VADIM GUSHCHIN, M.D., ARMANDO SARDI, M.D.

From the Division of Surgery, Section of Surgical Oncology, Institute for Cancer Care, Mercy Medical, Center, Baltimore, Maryland

Cytoreductive surgery/heated intraperitoneal chemotherapy (CRS/HIPEC) has been shown to be effective for selected patients with advanced appendiceal cancer. We propose that delaying CRS/HIPEC leads to disease progression and affects outcome. A retrospective analysis of a prospective database was carried out. Patients were divided into two groups based on time from diagnosis to CRS/HIPEC (less than 6 months = early, greater than 6 months = delayed). Comparison was made of Peritoneal Cancer Index (PCI), Prior Surgery Score (PSS), complete cytoreduction (CC), and lymph node status. Overall survival (OS) was calculated using Kaplan-Meier estimates. Of 127 patients, 50 had disseminated peritoneal adenomucinosis and 77 had peritoneal mucinous carcinomatosis (PMCA). Of patients with PMCA, 41 had early CRS/HIPEC and 36 delayed. PCI was less than 20 in 46 and 17 per cent ($P = 0.007$) of the early and delayed groups, respectively. CC was achieved in 88 and 61 per cent ($P = 0.009$) of the early and delayed groups, respectively. PSS was (2 of 3) in 51 and 91 per cent ($P = 0.001$) of the early and delayed groups, respectively. Five-year OS was 54 per cent for the early group and 45 per cent for the delayed group ($P = 0.2$). Delaying CRS/HIPEC was associated with higher tumor load and lower chance for complete cytroreduction. Longer follow-up and larger numbers are needed to determine if OS difference will reach statistical significance.

NEOPLASMS OF THE appendix are rare and frequently present at an advanced stage with peritoneal metastases. They are usually diagnosed after surgical exploration either to establish a diagnosis or to alleviate symptoms, resulting in either major debulking surgery or limited resection of metastases and appendectomy. After the diagnosis is established, some patients are referred to a peritoneal surface malignancy center for evaluation for cytoreductive surgery/heated intraperitoneal chemotherapy (CRS/HIPEC). Others receive systemic chemotherapy on a palliative basis with regimens used in the treatment of advanced colon cancer and may undergo further surgery if they become symptomatic, usually from intestinal obstruction.

The National Comprehensive Cancer Network (NCCN) treatment guidelines still include appendix cancer under colon cancer guidelines. These advocate systemic chemotherapy as a first line treatment for patients with peritoneal metastases in contrast to what has been more recently published about appendix cancer. The role of systemic chemotherapy in treating patients with appendiceal cancer is neither well studied nor reported,[1–4] whereas CRS/HIPEC has been extensively reported with meaningful long-term survival.[5–12] In addition, it is known that appendix cancer behaves differently than colorectal cancer, which has prompted a separate staging for appendiceal cancer in the most recent edition of the American Joint Commission Staging Manual.[13]

The controversy in treatment recommendations can lead to delay in CRS/HIPEC. We propose that the delay in CRS/HIPEC leads to disease progression and, therefore, adversely affects outcome.

Methods

Patients with appendiceal cancer and peritoneal spread who underwent CRS/HIPEC between the years of 1999 and December 2010 were identified from a prospectively collected database. Ronnett's histopathological classification was used to divide patients into two groups, disseminated peritoneal adenomucinosis

Presented at the Annual Scientific Meeting and Postgraduate Course Program, Southeastern Surgical Congress, Birmingham, AL, February 11–14, 2012.

Address correspondence and reprint requests to Hatem El Halabi, M.D., Fellow, Surgical Oncology, Mercy Health Services, Baltimore, MD 21202. E-mail: hhalabi@mdmercy.com.

(DPAM) and peritoneal mucinous carcinomatosis (PMCA),[14, 15] The PMCA intermediate category was included under PMCA. Computed tomography (CT) scan of the chest, abdomen, and pelvis and tumor markers (carcinoembryonic antigen, CA19-9, CA 125) were obtained before surgery. After review of the CT scan and patient's functional status (Eastern Cooperative Oncology Group = 0,1), surgery was recommended for patients with no extraperitoneal metastases if complete cytoreduction (CC) was felt to be feasible. The Peritoneal Cancer Index (PCI), as previously described by Jacquet et al., was used to assess the extent of peritoneal involvement.[16] Prior Surgery Score (PSS) was used as a measure of extent of previous surgery.[16] Lymph node (LN) status was obtained from patient's previous surgeries and at the time of CRS/HIPEC. A single surgeon performed all operations. The histopathology from CRS/HIPEC as well as from the first surgery or biopsy was reviewed at our institution when available.

Of 150 patients with appendiceal neoplasms and peritoneal spread who underwent CRS/HIPEC, 127 patients had their first CRS/HIPEC at our institution and constituted the study population. Of the other 23 patients, CRS/HIPEC was not performed as a result of extensive small bowel involvement at exploration precluding CRS/HIPEC in 16, whereas seven had undergone previous CRS/HIPEC at another institution. Patients with PMCA and DPAM were studied in separate groups. Each group was divided arbitrarily into two subgroups based on the time from diagnosis to CRS/HIPEC. The early group underwent CRS/HIPEC less than 6 months from diagnosis, whereas the delayed group had CRS/HIPEC 6 months or more after diagnosis. Comparison between the early and delayed group was made using the following parameters: age, sex, PCI, PSS, CC, LN status, and precytoreduction systemic chemotherapy administration.

No patients have been lost to follow-up. Details of the operation and intraperitoneal chemotherapy have been previously reported.[17, 18]

The data were collected prospectively during the patients' follow-up visits. Mean follow-up was calculated from the date of surgery until death or last follow-up visit. Comparisons between groups were performed using the χ^2 test for categorical variables and the analysis of variance for continuous variables. Relapse-free survival (RFS) was defined as no evidence of disease by physical examination, CT scan, or tumor markers only in patients who had complete cytoreduction. Overall survival (OS) was calculated from the date of CRS/HIPEC to the date of death or last encounter. RFS was calculated from the date of CRS/HIPEC to date of recurrence. 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. Results were considered statistically significant if $P < 0.05$. All patients signed a tissue and research consent through a protocol approved by the Institutional Review Board.

Results

Among the 127 patients, 77 had PMCA and 50 had DPAM. Mean follow-up was 31 months (range, 3 to 90 months).

Demographics and characteristics of the patients with DPAM in the early and delayed groups are summarized in Table 1. Five-year OS among early and delayed groups were 90 and 76 per cent, respectively ($P = 0.8$). Seven of 50 patients were dead at the time of analysis; five died of other causes and two died of disease (both in the delayed group).

Demographics and characteristics for the patients with PMCA among early and delayed groups are summarized in Table 2. Five-year OS was 54 per cent in the early group and 45 per cent in the delayed group ($P = 0.2$) and 5-year RFS was 52 and 38 per cent ($P = 0.4$) in the early and delayed groups, respectively.

Among the patients with PMCA, 14 of 41 (34%) in the early group had relapse. Eleven patients of 14 were not amenable to repeat cytoreduction and all 11 were dead from disease at the time of this analysis. Three patients had repeat CRS/HIPEC, one is alive with no evidence of disease after a third CRS/HIPEC, one is dead of disease, and one is alive with disease. In the delayed group, 16 of 36 (44%) had relapsed during our follow-up period. Thirteen of 16 were not candidates for repeat cytoreduction and all died of disease at the time of this analysis. Three patients had repeat CRS/HIPEC.

TABLE 1. *Demographics and Characteristics of Patients with Disseminated Peritoneal Adenomucinosis (DPAM) in the Early and Delayed Groups*

	Early Group	Delayed Group	*P* Value
Number	22	28	
Mean age at diagnosis (years)	53.0	51.0	
Mean age at surgery (years)	53.2	54.0	
Percent females	64%	64%	0.3
Prior surgery score PSS (2/3)	50%	79%	0.04
Peritoneal cancer index percent less than 20	9%	18%	0.4
Percent with complete cytoreduction	100%	79%	0.03
Mean duration of surgery	9.0 hours	10.5 hours	0.1

PSS, prior surgery score.

TABLE 2. *Demographics and Characteristics of Patients with Peritoneal Mucinous Carcinomatosis (PMCA) in the Early and Delayed Groups*

	Early Group	Delayed Group	*P* Value
Number	41	36	
Mean age at diagnosis (years)	51.5	49.1	
Mean age at surgery (years)	51.8	52.4	
Percent females	51%	64%	0.3
Prior surgery score PSS (2/3)	51%	91%	<0.001
Peritoneal cancer index percent less than 20	46%	17%	0.007
Percent with lymph node metastases	46%	41%	0.7
Percent with complete cytoreduction	88%	61%	0.009
Mean duration of surgery	9.7 hours	11.2 hours	0.05
Percent that received precytoreduction systemic chemotherapy	24%	57%	0.004

PSS, prior surgery score.

Two are alive with no evidence of disease and one has died of disease.

Discussion

Appendiceal neoplasms are heterogeneous and present usually with peritoneal metastases.[12] The prognosis of patients who undergo CRS/HIPEC depends on many parameters. Histopathology, CC, PSS, PCI, and LN status have been shown to be important prognostic factors.[12] In this study we separated patients into DPAM and PMCA to control for outcomes related to histopathology. The delayed group of patients with DPAM had a lower chance for CC and lower OS (Table 1); however, DPAM is usually an indolent disease and much longer follow-up is needed to compare outcomes between the delayed and early groups. Our further discussion will focus on patients with PMCA only.

The percentage of patients having undergone major debulking surgery, major resections that did not aim at complete cytoreduction before our cytoreductive surgery and HIPEC procedure, was 91 and 51 per cent in the delayed and early groups, respectively ($P < 0.001$). Major debulking surgery before cytoreductive surgery has been shown to have an adverse effect on the patients' outcomes.[16, 19] Any attempt at debulking or cytoreduction in patients with PMCA should aim at complete cytoreduction, that is, removal of all visible disease with residual tumor nodules measuring less than 2.5 mm. This practice is known to be essential for meaningful long-term survival. Previous major surgery not only delays the appropriate treatment, but also makes an already complicated surgery (CRS/HIPEC) more difficult and complex as a result of adhesions and disruption of normal anatomy. This opinion is supported by significantly prolonged duration of surgery in delayed patients with PMCA (mean prolongation of 1.5 hours [$P = 0.05$]). Therefore, we recommend that, at the time of exploration to establish a diagnosis in patients with peritoneal metastases, the procedure be limited to a simple biopsy or appendectomy, if feasible, followed by immediate referral to a peritoneal surface malignancy center for evaluation.

In the delayed group, 57 per cent of the patients had precytoreduction systemic chemotherapy, whereas that percentage was 24 per cent in the early group ($P = 0.004$). The few reported studies on systemic chemotherapy on a palliative basis for patients with peritoneal metastases from appendiceal cancer suggested an adverse outcome and did not recommend its routine use.[1, 2] In contrast, there are many reports about CRS/HIPEC in the treatment of appendiceal cancer with peritoneal metastases and experts in that field consider CRS/HIPEC as standard of care.[1, 2, 5–11, 20, 21] Despite this, the NCCN treatment guidelines still include appendiceal cancer under the recommendations for colon cancer and recommend systemic chemotherapy as first-line treatment for patients with peritoneal metastases without mention of cytoreductive surgery. We believe that these recommendations are promoting systemic chemotherapy on a palliative basis without consideration for CRS/HIPEC and therefore could lead to delaying referral to a peritoneal surface malignancy center where multidisciplinary care for this rare disease is feasible. We recommend a change in these guidelines to underscore the importance of CRS/HIPEC as first-line treatment for patients with peritoneal metastases from an appendiceal cancer primary.

The delay in CRS/HIPEC was associated with statistically significant lower chance for complete cytoreduction (Table 2). Complete cytoreduction has been shown to be essential for long-term survival by multiple previous investigators.[6, 8, 11, 12] In addition, the delayed group had statistically higher PCI scores suggesting progression of disease because of delaying surgery (Table 2). A higher PCI score has been also shown to affect survival.[11, 16, 19] Extensive disease could also make CRS/HIPEC more complex and complicated, hindering efforts at complete cytoreduction. The difference in PCI and CC did not translate into a statistically significant difference in OS or RFS among groups. However, there was a trend for better OS and RFS in the early group. A larger number of patients and longer follow-up may reveal a statistically significant difference.

There are several limitations to this study that should be addressed. The retrospective nature lends an inherent bias as does patient selection. The numbers of patients

involved are small and the follow-up time is also fairly short. The 6 months' time was arbitrarily chosen and some patients in each group were close to the 6-month interval. We tried to control for histopathology by dividing patients into PMCA and DPAM; however, it is known that there is variation in biology and aggressiveness of disease among each group and those are not accounted for in this study. That variation could have lead to different presentation of the disease that dictated the initial management with either precytoreduction systemic chemotherapy and/or major debulking surgery. However, in this retrospective analysis, such factors were difficult to evaluate.

In conclusion, delaying CRS/HIPEC in patients with PMCA is associated with higher volume disease and possible disease progression that significantly lowered the chance for complete cytoreduction and, consequently may affect the final outcome for patients with peritoneal metastases from appendiceal cancer.

REFERENCES

1. Smith JW, Kemeny N, Caldwell C, et al. Pseudomyxoma peritonei of appendiceal origin. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1992;70:396–401.

2. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. Ann Surg 1994;219:112–9.

3. Sugarbaker PH, Bijelic L, Chang D, Yoo D. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. J Surg Oncol 2010; 102:576–81.

4. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer 2010;116:316–22.

5. Chua TC, Yan TD, Smigielski ME, et al. Long-term survival in patients with pseudomyxoma peritonei treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy: 10 years of experience from a single institution. Ann Surg Oncol 2009;16:1903–11.

6. Elias D, Honore C, Ciuchendea R, et al. Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Br J Surg 2008;95:1164–71.

7. Levine EA, Stewart JH, Russell GB, et al. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: experience with 501 procedures. J Am Coll Surg 2007;204:943–53.

8. Omohow C, Nieroda CA, Studeman KD, et al. Complete cytoreduction offers long-term survival in patients with peritoneal carcinomatosis from appendiceal tumors of unfavorable histology. J Am Coll Surg 2009;209:308–12.

9. Verwaal VJ, Van Ruth S, De Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.

10. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426–32.

11. Elias D, Gilly F, Quenet F, et al. Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. Eur J Surg Oncol 2010;36:456–62.

12. Sugarbaker PH. Epithelial appendiceal neoplasms. Cancer J 2009;15:225–35.

13. Edge SB, Byrd DR, Compton CC, et al. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th ed. New York, NY: Springer; 2010:133.

14. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to 'pseudomyxoma peritonei.' Am J Surg Pathol 1995; 19:1390–408.

15. Ronnett BM, Yan H, Kurman RJ, et al. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer 2001; 92:85–91.

16. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359–74.

17. El Halabi H, Gushchin V, Francis J, et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal cancer and extensive disease. Ann Surg Oncol 2012;19:110–4.

18. El Halabi H, Gushchin V, Francis J, et al. Prognostic significance of lymph node metastases in patients with high-grade appendiceal cancer. Ann Surg Oncol 2012;19:122–5.

19. Sugarbaker PH. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999;6:727–31.

20. Esquivel J, Elias D, Baratti D, et al. Consensus statement on the locoregional treatment of colorectal cancer with peritoneal dissemination. J Surg Oncol 2008;98:263–7.

21. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol 2006;7:69–76.