UNIVERSITY OF CALIFORNIA,
IRVINE

Analysis of Oncologic Outcomes Associated with Anti-adhesion Sodium Hyaluronate-Carboxymethylcellulose Barrier Following Optimal or Complete Cytoreductive Surgery for Ovarian, Fallopian Tube, and Peritoneal Cancers

THESIS

Submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Lauren Krill, MD

Thesis Committee:
Professor Sherrie Kaplan, Chair
Professor Sheldon Greenfield
Professor Robert Bristow

2014

DEDICATION

This work is dedicated to my loving and supporting husband.

"Where this is love there is life."
-Mohandas Ghandi

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ACKNOWLEDGMENTS

I would like to express heartfelt appreciation to my committee chair, Professor Sherrie Kaplan and to committee member, Professor Shelly Greenfield for their guidance and support. Their enthusiasm and dedication to the MS-BATS curriculum has given life to an academically rigorous and intellectually stimulating, interdisciplinary clinical research program. They have devoted themselves to training physician-scientists and researchers to work together to improve how we conduct comparative effectiveness research, assess and improve healthcare quality, and transform biomedical discoveries into evidenced-based medicine. I am sincerely grateful to have had the opportunity to participate in this academic endeavor with such wonderful teachers and national leaders in clinical research.

In addition, my sincerest gratitude to Professor Dr. Robert Bristow, who has been my mentor for many years, whose integrity, intelligence, determination, and vision have had lasting effect on me as a trainee and future gynecologic oncologist. It is an honor and privilege to work with you.

Also, I am grateful to Dr. Philip Di Saia for supporting me and encouraging me to pursue an advanced degree in clinical research through the MS-BATS program. His leadership, compassion and tireless work ethic are an inspiration to everyone who is fortunate enough to have trained at the University of California, Irvine under his legacy.

I would also like to thank my collaborators, whose hard work, diligence and mentorship made this study possible, Dr. Kristine Penner, Associate Professor University of California, Irvine, and most importantly my colleague Melissa Gerardi and Dr. Amanda Nickles Fader, Director of the Kelly Gynecologic Oncology Service, at the Johns Hopkins Hospital.

Financial support was provided by the Division of Gynecologic Oncology institutional NIH T-32 training grant (Ruth L. Kirschstein NRSA Institutional Training Research Grant, 2T32 CA-060396-11).

ABSTRACT OF THE THESIS

Analysis of Oncologic Outcomes Associated with Anti-adhesion Sodium Hyaluronate-Carboxymethylcellulose Barrier Following Optimal or Complete Cytoreductive Surgery for Ovarian, Fallopian Tube, and Peritoneal Cancers

By

Lauren Krill

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2014

Professor Sherrie Kaplan, Chair

Objectives: Hyaluronan is a component of the anti-adhesive barrier HA-CMC and has been implicated in tumor growth and metastasis. The study aim was to determine if HA-CMC use is associated with adverse effects on disease progression or survival in patients undergoing surgical cytoreduction for primary treatment of advanced ovarian, fallopian tube, and peritoneal cancers.
Methods: Retrospective cohort study of patients undergoing optimal or complete cytoreduction between 1/95-12/08. The primary endpoints were progression free survival (PFS) and overall survival (OS). Fisher's exact test, Kaplan Meier survival analysis, and multivariate Cox proportional hazards regression were utilized.

Results: Two hundred eighty-eight cases were analyzed; HA-CMC was utilized in 130 procedures (45%). On univariate analysis, HA-CMC was associated with complete cytoreduction, high surgical complexity score, good performance-status, and being alive at last follow-up (all $p<0.05$). Neither PFS nor OS was significantly different between subjects with or without HA-CMC (median PFS 16.8 versus 16.4 months, p=0.38; median OS 40.6 versus 36

months, P=0.34). PFS was significantly shorter amongst high-risk subjects, independent of HA-CMC use, with age ≥50, Stage IV disease, PS ≥1, visible residual disease, or interval cytoreduction (all $p<0.05$). Additionally, major postoperative complications and platinum resistance were associated with shorter OS ($p<0.05$). After controlling for confounding factors using multivariate Cox proportional hazards regression, HA-CMC use did not independently predict PFS (HR 1.10; 95% CI:0.83-1.45) or OS (HR 0.98; 95% CI:0.73-1.32).

Conclusions: HA-CMC adhesion barrier placement at the time of primary or interval cytoreductive surgery for ovarian, fallopian tube, and peritoneal cancer does not impact recurrence or survival outcomes.

CHAPTER 1: INTRODUCTION

Appropriate surgical candidate selection and maximum surgical effort are critical to the management of advanced ovarian cancer. The purpose of this retrospective cohort study is to determine what effect the use of the anti-adhesion barrier, sodium hyaluronate-carboxymethylcellulose (HA-CMC) may have on disease recurrence or survival following primary or interval cytoreductive surgery for the treatment of advanced ovarian, fallopian tube, and peritoneal cancers. HA-CMC is a bioresorbable membrane that is used to prevent the formation of scar tissue after surgery by acting as a temporary physical barrier between traumatized tissue surfaces. This disrupts the pathogenesis of peritoneal fibrosis that causes adhesions and allows the normal healing process and re-epithelialzation to occur. One of the chemical components, hyaluronan (HA), is a high molecular weight polysaccharide found in the extracellular matrix, known to promote cellular adhesion, migration and proliferation. There is some evidence using in vitro cancer models to suggest that endogenous hyaluronan plays an important role in tumor growth, invasion and metastasis as well, thus raising the theoretical concern that HA-CMC as an exogenous source of HA may have negative implications for tumorigenesis in patients with cancer. The current research also explores the potential interaction between HA-CMC, residual disease, surgical complexity and other confounding factors common to ovarian cancer surgery in order to determine if there are cumulative adverse effects on cancer recurrence or mortality.

Specific Aim # 1: To determine the impact HA-CMC placement may have on the risk of cancer recurrence after primary debulking surgery for ovarian cancer.

Hypothesis # 1: HA-CMC does not negatively impact progression free survival. Ovarian cancer recurrence will not occur earlier in patients who have had HA-CMC placement at the time of surgery.

Specific Aim #2: To compare overall survival for patients with ovarian cancer who were and were not exposed to HA-CMC.

Hypothesis # 2: There is no difference in all-cause mortality in patients who are exposed to HA-CMC during cytoreductive surgery for ovarian cancer.

Specific Aim # 3: To examine the interaction between HA-CMC and residual tumor remaining after surgery and the impact this has on progression free survival.

Hypothesis # 3: There will be no difference in the persistence of disease or interval to cancer recurrence after surgery between patients who undergo optimal ($\leq$10mm) debulking versus complete cytoreduction (no gross residual disease) based on HA-CMC use intraoperatively.

CHAPTER 2: BACKGROUND

Ovarian cancer often presents with advanced stage disease in most women; it is the leading cause of death from gynecologic cancers and will be responsible for approximately 14,000 women losing their lives this year in the United States.[1] Treatment typically consists of upfront debulking surgery followed by adjuvant platinum-based chemotherapy. Several studies have established that the best outcomes for these patients are achieved through complete primary cytoreduction/debulking surgery with the intention of removing of all visible disease. [2,3] Consequently, over the years comprehensive surgeries for this malignancy have evolved from simple hysterectomy and bilateral salpingo-oophorectomy (BSO) to include radical oophorectomy with peritonectomy (where the peritoneal lining is stripped away from all surfaces in the abdomino-pelvic cavity) and multiple organ resections frequently involving the bowel and upper abdomen.[4] The radical nature of these procedures predisposes patients to the development of postoperative adhesions—a long recognized problem in this population associated with increase morbidity, mortality, and cost.[5]

In an effort to reduce these risks, gynecologic oncologists often utilize commercially available anti-adhesion barriers, such as sodium hyaluronate-carboxymethylcellulose (HA-CMC), which is a bioresorbable membrane that has been shown to decrease the incidence and severity of postoperative scar tissue following intraoperative placement.[6] The utility of HA-CMC in advanced ovarian cancer has been demonstrated in a prospective trial of intraoperative placement following radical oophorectomy and pelvic peritonectomy—a significant decrease in the extent and density of pelvic adhesions was successfully observed at the time of second-look

laparoscopy.[6] The rate of microscopically positive pelvic disease in this study was 7.1% that they claimed is consistent with other reports in the literature and thus HA-CMC demonstrated no adverse effect disease persistence locally.[6] The author also later performed a cost-benefit analysis of HA-CMC utilization in an adhesion prevention strategy for another gynecologic malignancy, cervical cancer, which appeared to be cost-effective not only from a societal perspective but also that of third-party payers.[7] Other retrospective studies that support the safety and efficacy of HA-CMC in gynecologic oncology with no major adverse events reported, but it may come at the expense of higher rates of subsequent intra-abdominal fluid collections, which may or may not be clinically relevant.[8-10] Overall the risks and benefits for every patient must be weighed individually but there are several potential gains that are particularly relevant to this study population. Clinical trials have shown that HA-CMC decreases the difficulty of reoperations, operative time and risk of bowel injury during subsequent surgeries. Patients with ovarian cancer may require multiple operations or intraperitoneal (IP) procedures, including the administration of IP chemotherapy directly into the abdomen, which has become part of the first-line management for advanced ovarian cancer. Adhesions are also frequently implicated in the etiology of small bowel obstruction (SBO) and chronic pelvic pain in some patients.[11] SBO is a common occurrence in the natural history of ovarian cancer, usually due to progressive disease, but adhesions could also be a modifiable contributing factor. In the general surgery literature, there is some Level I evidence purporting that HA-CMC significantly reduces the need for reoperation for adhesive small bowel obstruction. [12]

However, there are several concerns raised by theoretical risks of tumorigenesis presented by historical *in vitro* studies and conflicting pre-clinical data from *in vivo* cancer models. Hyaluronan (HA), is a major component of HA-CMC and has been implicated in tumor

growth and spread, many are concerned it may also provide a stable matrix for proliferation of tumor cells.[13-15] Also, HA is a major ligand of CD44, a major cell surface receptor expressed by a wide variety of normal tissues but it is also expressed in cancer stem cells and many solid malignancies, including ovarian cancer.[16,17] Hence, the concern becomes that IP administration of HA might improve tumor cell adhesion by providing numerous sites for HA-CD44 interaction and enhances tumor growth, motility, and metastasis in a dose-dependent fashion.[18] However, Puccarelli et al. showed that HA-CMC had no statistically significant adverse affect on colon cancer implantation or risk of postoperative death in a murine model using IP inoculation with tumor cells.[15] These findings have been confirmed by other investigators.[19,20] Although, there are some studies that have strongly implicated HA in tumorigenesis and angiogenesis, the role of HA in cancer may be more complex than anticipated. How HA processing is affected by cancer is not completely understood. Higher molecular weight HA appears to be inhibitory and hyaluronidase (produced by tumor cells) may play a role in tumor suppression and mediating chemo-resistance. However, HA processing might also explain the contradictory results about exogenous HA in the published literature.[21]

Several prospective randomized controlled trials have provided evidence that HA-CMC appears to be safe and does not appear to affect recurrence or survival rates in humans undergoing colorectal surgery for cancer.[22,23] Oikonomakis et al. showed no detriment to short-term oncologic outcomes using HA-CMC in 63 patients undergoing curative operations for colorectal cancer.[24] Unfortunately, there is a paucity of research on this topic specifically in the field of gynecologic oncology and the effect of HA-CMC on ovarian cancer recurrence remains unknown. Therefore, the objectives of the current study are to identify if the use of HA-CMC has a negative impact on survival or increases the risk of cancer recurrence. The hypothesis is that

the placement of HA-CMC intraoperatively would not be associated with adverse effects on disease progression or survival in patients undergoing primary or interval debulking surgery for ovarian cancer.

CHAPTER 3: METHODS

Research Design and Study Sample

Approval to conduct this study was obtained from the Johns Hopkins Medical Institutions Clinical Research Committee (NA#00021845) the requirement for informed patient consent was waived and the investigation of the de-identified dataset was deemed exempt by the University of California, Irvine Institutional Review Board (HS#2014-1211). The study design is a single institution cohort study. The data was collected retrospectively. The study population includes all patients who underwent optimal ($\leq$ 10 mm or $\leq$ 5 mm) or complete (no gross residual disease) cytoreduction during primary or interval debulking for Stage III and IV epithelial ovarian, fallopian tube and primary peritoneal carcinoma between January 1995 and December 2008. An existing cancer registry was previously used to identify eligible cases for inclusion from all the patients diagnosed with ovarian cancer and managed by the cancer center. This study sample was chosen because it is comprised of subjects who had procedures at least five-years ago to ensure long-term follow-up information were available after surgery in the de-identified database. The operations were performed by a board-certified gynecologic oncologist usually in conjunction with a gynecologic oncology fellow. The key independent variable—HA-CMC placement was carried out at the discretion of the attending surgeon and documented in the operative note.

Inclusion was restricted to patients who underwent optimal cytoreduction at the Johns Hopkins Hospital during the study period. The institutional and divisional practice at the time was to avoid using HACMC in patients with suboptimal (>1cm) residual disease and thus they were excluded from the study as they were not eligible to receive the exposure. Additionally, nine cases for which no operative note was available were also excluded.

Study Variables

The experimental group was exposed to HA-CMC during their primary surgery but the control group (No-HACMC) was not. Details of the operation including HA-CMC utilization, amount of residual disease and procedures performed (e.g. total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and/or para-aortic lymph node dissection, diaphragm peritonectomy or resection, small or large bowel resection, splenectomy, distal pancreatectomy, liver or gastric resection, cholecystectomy, and placement of intraperitoneal pelvic drains or catheters) were obtained by trained research assistants from the electronic operative report that is dictated by the attending surgeon. Assessments of residual disease were determined by attending surgeons at the end of the operation and refer to the size of any visible metastatic tumor implants remaining at the termination of the procedure that by convention are categorized into three groups: no gross residual disease (NGRD), macroscopic implants $\leq$ 5mm or $\leq$ 10 mm in size. Length of stay, hospital course including the presence or absence of major postoperative complications, and adjuvant therapy received were extracted from the electronic medical records (e.g. discharge summaries, inpatient and outpatient progress notes, pathology, laboratory and radiology reports etc.). Major postoperative complications assessed included pelvic abscess (with radiographic documentation), infection requiring intravenous antibiotics or

extension of hospitalization, prolonged ileus (≥3 days), EBL >1 liter, thromboembolic events (deep vein thrombosis or pulmonary embolism), myocardial infarction, pneumonia, pleural effusion requiring thoracentesis, bowel anastomotic leak or fistula, sepsis, re-operation, unplanned hospital readmission, and death within 30 days of surgery. Gynecologic oncologists from the Mayo Clinic have developed a strategic approach to quantify the complexity of these operations in order to facilitate communication and research.[25] The surgical complexity score (SCS) was calculated by the gynecologic oncology fellow based on the total points assigned for the level of complexity and the number of surgical procedures performed in accordance with those criteria (see Appendix A). The SCS is further stratified into ordinal SCS Risk Categories based on the total sum of points: low (3 points), intermediate (4-7 points), and high (≥8 points).

Additional demographic patient and tumor characteristics obtained from electronic charts were limited to the following to protect patient privacy: age at surgery, race, International Federation of Gynecology and Obstetrics (FIGO) tumor stage and grade, histology, pre-operative albumin level, American Society of Anesthesiologists (ASA) classification and Eastern Cooperative Oncology Group (ECOG) performance status.[26,27] Generally, ASA classification and ECOG performance status (PS) are used as proxy indicators of medical co-morbidity and functional capacity (see Appendix B). If patients eligible for the study were treated with neoadjuvant chemotherapy (NACT), that was also documented in the dataset. This means the patients may have had several cycles of chemotherapy prior to surgery and these operations are referred to as interval debulking surgeries; as opposed to primary debulking surgery when patients have surgery first and receive chemotherapy postoperatively. Information was also collected on adjuvant treatments received postoperatively that typically consisted of platinum

and taxane-based combination chemotherapy administer either intravenously (IV) or intraperitoneal (IP).

Study Outcomes

The primary endpoints of interest were median progression free survival (PFS) and median overall survival (OS). These time-to-event dependent variables were measured in months from the date of surgery to the date of recurrence and date of death, respectively. For censored cases, the date of last visit was used to calculate survival in the patients who had not experienced relapse, death or were lost to follow-up. Patient's who experienced recurrence of their disease more than 12 months after completion of their last cycle of cytotoxic chemotherapy were considered platinum sensitive and between 6-12 months are categorized as intermediate. Patients who relapse within 6 months or who progress during treatment were considered platinum resistant. In order to minimize attrition due to missing data (e.g. survival for patients transferred to hospice care or receiving treatment at outside facility) and to improve the accuracy of quality assurance checks were performed by at least two research assistants and all-cause mortality data from the hospital records were verified using a national vital statistic registry—the social security death index.

Power Calculations and Statistical Analysis

Baseline characteristics of the exposed and the unexposed groups including demographic, tumor and surgical data were analyzed using Fisher's exact test and chi-squared test. For statistical purposes, some variables were stratified into categorical variables in the following manner: Age was divided into three groups (less than 50 years-old, ages 50 to 75, and 75 or

older) by convention and later when summary statistics were available the age groups were collapsed using the upper quartile as a cutoff to better define an older population. Patients were divided into two groups by ASA equal to 1 or 2, and 3 or 4 because this cut-off reflects a clinically meaningful decline in a patient's health status. Similarly, performance status was separated into groups with PS = 0 (normal) versus PS $\geq$ 1 (see Appendix B).

Kaplan-Meier estimation was used to construct the progression free and overall survival curves and survival comparisons were conducted using the log rank test. A two-sided log rank test with a total sample size of 288 would yield 90% power with alpha of 0.05 to detect a difference of 20% between the proportions surviving in each group with or without HA-CMC. Cox Proportional Hazards regression was employed for univariate and multivariate survival analyses. In order to adjust for several potential confounding factors that may impact survival any covariate with $p < 0.2$ on univariate analysis was included in the multivariate model. To identify those clinical parameters independently predictive of oncologic outcome, covariates were kept in the final multivariate regression equation if determined to be statistically significant after forwards and backwards elimination indicated their inclusion did not improve the predictions. The null hypothesis (H_0) was that there would be no difference in survival, PFS or OS, between patients who had HA-CMC placed during their surgery and those who were not exposed to HA-CMC (controls). Statistical analyses were performed using SPSS software (SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and *P* values < 0.05 are considered statistically significant.

CHAPTER 4: RESULTS

Demographic and Clinical Differences between Treatment Groups

Two hundred eighty-eight consecutive patients with Stage III or IV epithelial ovarian cancer were included in the analysis. HA-CMC was used in 130 cases (45%). The exposed and unexposed groups were similar with respects to age and race; the mean age of patients was 58.5 year in those who received HA-CMC and 59.8 in those without HA-CMC (P = 0.38) and the majority of patients in both groups were white (84.6% versus 79.1%; P = 0.39). Further baseline demographic and clinical data are summarized in Table 1.1. The groups had comparable distributions of patient with stage IV disease (24.6% versus. 26.0%; P = 0.8) and the majority of tumors showed serous histology (83.1% versus. 85.4%; P = 0.67). There was no difference between cohorts for those who recurred if surgery was performed for primary or interval debulking (P = 0.67). However, subjects exposed to HA-CMC were more likely to have healthy baseline performance status (PS = 0; defined as fully active and able to carry on all pre-disease performance without restrictions) and less severe ASA classifications. The HA-CMC group had 83.1% of patients whose PS = 0 compared to 69.0% in the unexposed group (P = 0.02). The control group (No-HACMC) had 17.7% of patients with ASA 3 or 4 which was significantly higher than the HA-CMC group at 7.7% (P = 0.04). Evidence of protein malnutrition was prevalent in both groups with approximately a third of patients having hypoalbuminemia (preoperative albumin level < 3 g/dL) (P = 0.46).

A comparison of surgical parameters according to HA-CMC use is shown in Table 1.2. Complete cytoreduction (NGRD) was performed in 84 (64.6%) and 69 (43.7%) surgeries with and without HA-CMC, respectively (P = 0.002). Univariate analysis revealed that patients in the

HA-CMC group were more likely to have High surgical complexity scores (P <0.001), pelvic and para-aortic lymphadenecotmy (P < 0.001) rectosigmoid resection (P = 0.01), splenectomy (P = 0.04), and diaphragm peritonectomy or resection (P < 0.001). There were no detectable differences between the treatment groups in major postoperative morbidity experienced within the first 30 days after surgery (OR=0.79; 95% CI, 0.48-1.31; P = 0.35).

Following surgery, there was no significant difference in the number of patients who received adjuvant chemotherapy (91% in HA-CMC group compared to 95% of controls; P = 0.16). Over 90% of patients were treated with combination platinum and taxane chemotherapy, predominantly carboplatin and paclitaxel, and the remainder were treated with additional or other agents as part of a clinical trial protocol (data not shown). However, more patients in the HA-CMC than control group received at least one cycle of IP chemotherapy (26.9% versus 3.2%; P < 0.001) as opposed to IV chemotherapy only.

Statistics on Patient Follow-up and Cancer Recurrence (Progression Free Survival)

The mean patient follow-up was 43.4 months in the HA-CMC group versus 48.5 months for controls (P = 0.26). At the time of last follow-up, more patients in the HA-CMC exposed group were alive compared to controls (37.7% versus 21.5%; P=0.003). The likelihood of ever-experiencing an ovarian cancer recurrence is the same in patients who had HA-CMC compared to those who did not receive HA-CMC, according to the unadjusted logistic regression model (83.1% versus 89.2%; OR=1.69; 95% CI, 0.86-3.37; P = 0.13). Kaplan Meier analysis indicated PFS did not significantly differ between subjects with or without HA-CMC use as demonstrated in Figure 1 (median PFS 16.8 versus 16.4 months, P = 0.36). PFS was significantly shorter amongst subjects 50 to 70 years of age, with Stage IV disease, impaired baseline performance

status (PS ≥1), visible residual disease, or interval cytoreduction on univariate analysis (see Table 2.1). The covariates resulting in P-value < 0.2 on the univariate analysis were included in the multivariate model. After controlling for confounding factors using Cox proportional hazards regression, HA-CMC use did not independently predict PFS (HR 1.10; 95% CI: 0.83-1.45; P =0.5) (see Table 2.1 again). The odds of recurrence are greater for patients who underwent interval debulking (HR 1.72; 95% CI: 1.23 – 2.41; P = 0.002) and were High SCS risk category (HR 1.36; 95% CI: 1.03 -1.79; P = 0.03). Complete cytoreduction (NGRD) was the only covariate associated with improved PFS (HR 0.73; 95% CI: 0.56-0.96; P = 0.02).

All-cause Mortality and Overall Survival

The cumulative five-year overall survival was 38.8% with HACMC and 35.9% in the control group, which did not significantly differ using the log-rank test (P = 0.33). Figure 2 shows that there was no difference between the treatment groups in median OS with 40.6 months in the HA-CMC group compared to 36 months without HA-CMC (P = 0.33). The results of the univariate analyses for OS are shown in Tables 2.2 and similarly to PFS: age, stage, PS, and NGRD were all significantly associated with OS (see Table 2.2). Additionally, major postoperative complications and platinum resistance were associated with shorter OS ($P< 0.05$). Again, all covariates resulting in P-value < 0.2 were included in Cox proportional hazard model. To create a parsimonious model, backwards elimination was used to identify variables that did not contribute to the prediction of OS. After controlling for confounding factors, the odds of death were not greater for patients exposed to HA-CMC; there was no statistical difference in all-cause mortality compared to the control group (HR 0.98; 95% CI: 0.73-1.32; P = 0.89). The variables shown to be negatively predictive of OS, independent of HA-CMC treatment group, were age ≥

70 (HR 1.65; 95% CI: 1.07-2.54; P = 0.02), PS≥1 (HR 1.85; 95% CI: 1.33-2.56; P = 0.001) and post-operative morbidity (HR 1.40; 95% CI: 1.04-1.89; P = 0.03). The odds of death were lower for patients with NGRD (HR 0.71; 95% CI: 0.53-0.95; P = 0.02) and complete cytoreduction was the only covariate associated with improved survival (median OS 50.4 versus 33.7 months, P = 0.01).

Residual Disease Sub-group Analysis

To determine whether there is harm (an increased number of recurrence events) associated with HA-CMC use for patients with macroscopic residual disease we performed a subgroup analysis with a formal test for interaction. There was no difference in recurrence rates or disease-free survival, in this subgroup, between HA-CMC treatment groups with HR of 0.88 (0.49 – 1.38). The *P* value for the interaction of HA-CMC and visible residual disease was 0.46 in the unadjusted Cox regression model. Figure 3 shows the survival curves in patients who have up to 10 mm of residual disease and there was no difference in median PFS between the HA-CMC and control groups (median PFS 15.1 versus 16.2 months; P = 0.26).

CHAPTER 5: DISCUSSION

Avoiding the development of postoperative adhesions in patients undergoing extensive debulking surgeries is an important motivating factor for many gynecologic oncologists and could be particularly helpful for patients with ovarian cancer for several reasons. First, these

patients are known to be at high-risk for scar tissue due to the nature of the radical procedures and abdomino-pelvic peritonectomy. Unfortunately, the natural history of this disease means that many of these patients are destined to develop SBOs in the future typically related to progressive IP disease. However, the use of HA-CMC as a preventive strategy to combat adhesions may help decrease adhesion related side effects such as abdominal pain, pelvic pain and reduce the risk of developing an adhesive-related small bowel obstruction. Furthermore, by preventing adhesions there is the potential to decrease the difficulty of reoperations due to scar tissue and to optimize the distribution of IP chemotherapy, improve the efficacy and improve tolerability (decrease the most common side effects of IP chemotherapy such as pain. There is strong evidence that HA-CMC is safe and effective in benign gynecology and other surgical sub-specialties but the majority of the published data on oncology outcomes have been conducted in patients with non-gynecologic cancers, predominantly colorectal cancer.

There are very limited empirical data available on the impact of HA-CMC on gynecologic cancers. Data from the current study suggests that the use of HA-CMC is not associated with a difference in the odds of disease progression or mortality in patients with ovarian, fallopian tube or primary peritoneal malignancies. This is the largest study to date in this population. Tan et al. also performed a retrospective study in a similar population with fewer patients, but they did include patients with suboptimal (> 1cm) residual disease (15% of the patients receiving HA-CMC). They also found no effect on cancer recurrence, survival, or postoperative complications rates.[28]

In the current study population, patient who underwent HA-CMC placement at the time of their surgery were more likely to have complete cytoreduction, high surgical complexity scores, less medical co-morbidity and better baseline performance status. It is possible that the

increased utilization of HA-CMC in these groups is heavily influenced bias by indication. Surgeons may be inclined to use it in patients they anticipate will receive IP chemo, although this study was not designed test the superiority of IP chemo and having had IP chemo was not an independent predictor of overall survival. Regardless, surgeon preference may promote selection bias e.g using HA-CMC it in patients with minimal residual disease who are expected tolerate aggressive surgery well and have an uncomplicated recovery. These variables may interact with HA-CMC to influence patient outcomes and masking harmful effects in patients who are going to do well regardless, however, we were able to adjust for these confounding variables in our multivariate model and still found no detectable harms.

Based on our data there is no adverse effect of HA-CMC on persistence of disease, recurrence or mortality in ovarian cancer. However, HA-CMC was used more often in patients with no gross residual disease. Initially, clinicians at our institution believed HA-CMC use was contraindicated in patients with significant residual disease given the unknown effects on progression, tumor proliferation and metastasis of remaining tumors cells. One of the limitations of this study is that fewer patients in the experimental group did not have appreciable residual disease and our results cannot be generalized to suboptimal debulking and is potential underpowered to detect small differences based on HA-CMC with more significant volumes of residual disease even with optimally debulked patients (up to 10 mm). Unfortunately, the current study is too small to support a stratified analysis based on the amount of residual disease. However, the half life of this product is relatively short. It is reabsorbed within 7 days and for that reason it is unlikely to have lasting pro- or anti-tumor effects.

Other limitations include the retrospective nature of the study and the inherent risks of inaccuracy in studies relying on chart review. Fortunately, the electronic medical record was

established throughout the study period but it is heavily reliant on accurate documentation. To ensure quality control the integrated database and tumor registry are maintained by multiple coders who perform quality checks and ensure the completeness of the dataset, which was successful in minimizing missing data. Despite these limitations the current analysis adds to the growing body of oncologic literature in regards to surgical adjuncts such as anti-adhesion barriers. We have shown that HA-CMC has no adverse effects on oncologic outcomes in patients with ovary cancer.

One of the strengths of the current study is that response to platinum based chemotherapy and amount of residual disease after surgery were the strongest prognostic indicators of survival. It is reassuring that the present model is consistent with the published literature on the most reliable predictors of improved survival and after adjusting for these factors there was still no difference between treatment groups. The one variable we were not able to adjust for in the final model was platinum resistance as it is time-dependent variable defined by the length of progression free survival (our outcome of interest). However, it is not useful in our HA-CMC model because it is a proxy for outcome that is not available at the time this treatment decision is made. Also, the current study is too small to support a stratified analysis of platinum resistant and platinum sensitive events. On the other hand, our sample size is sufficient to detect a clinically significant difference in our primary endpoints if it exists based on our power calculations mentioned previously. This study supports the hypothesis that HACMC does not negatively impact the risk of disease recurrence or survival in the patients we studied.

CHAPTER 6: SUMMARY AND CONCLUSIONS

The results of the current study show that there is no deleterious effect of HA-CMC on oncologic outcomes for patients with ovarian cancer. These data are consistent with evidence available in other surgical oncology subspecialties that there are no significant harms associated with HA-CMC use. Furthermore, there are significant potential benefits that remain unstudied in gynecologic malignancies that should be the target of future studies. In conclusion, HA-CMC appears to be safe when used for prevention of adhesions in patients with optimally debulked advanced ovarian, fallopian tube or primary peritoneal carcinomas.

FIGURE No. 1

Figure 1. Median Progression Free Survival in patients with and without HA-CMC.

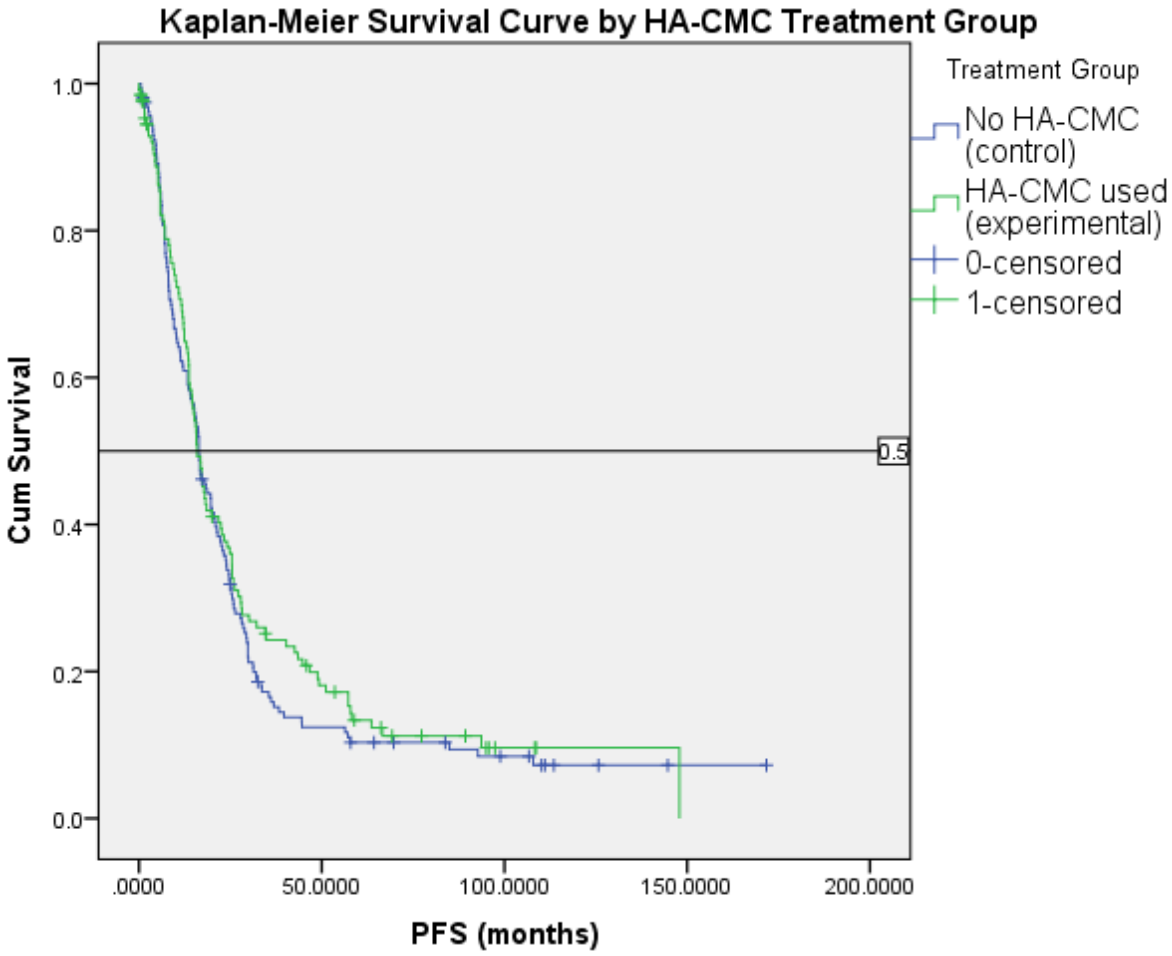

FIGURE No. 2

Figure 2. Median Overall Survival in patients with and without HA-CMC.

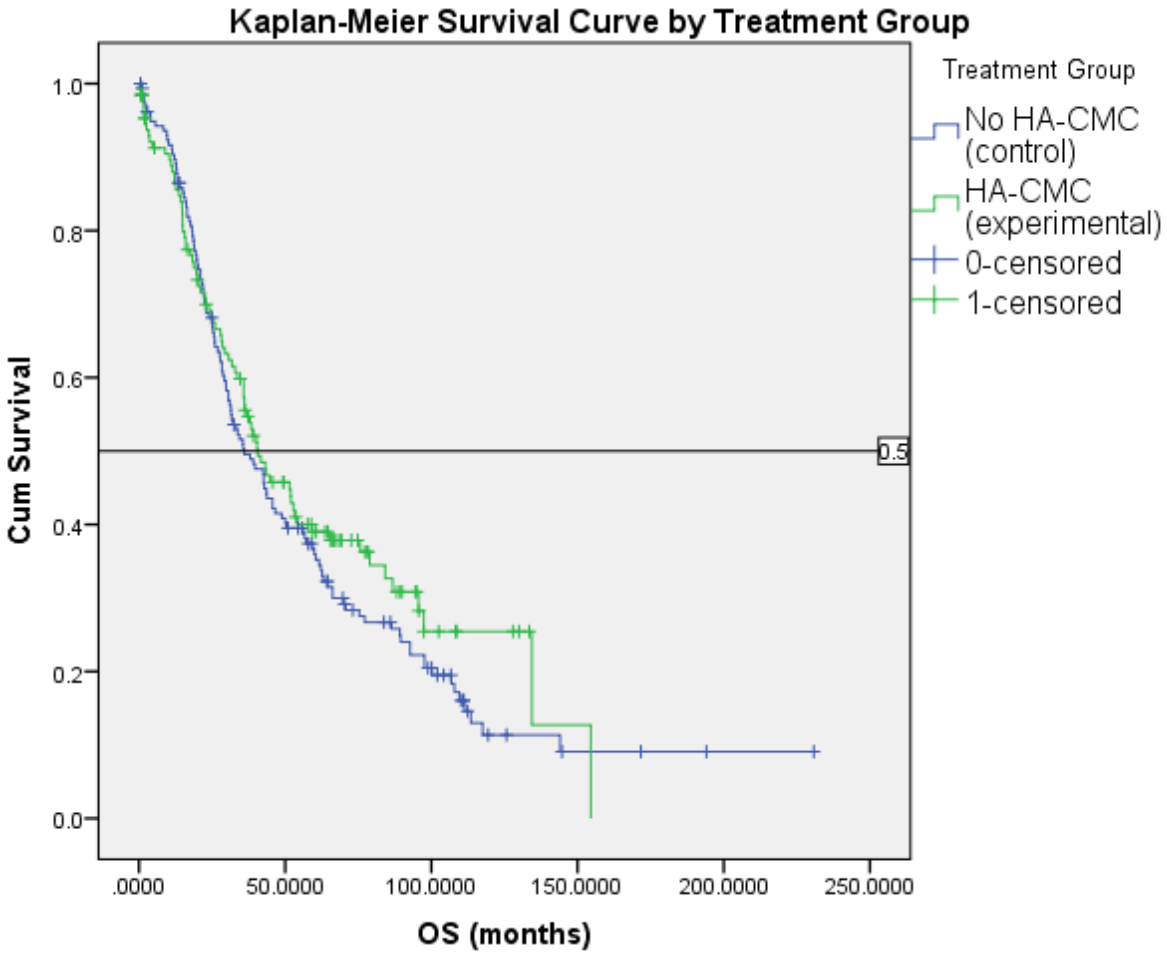

FIGURE No. 3

Figure 3. Survival curves stratified by HA-CMC placement in patients with visible residual disease.

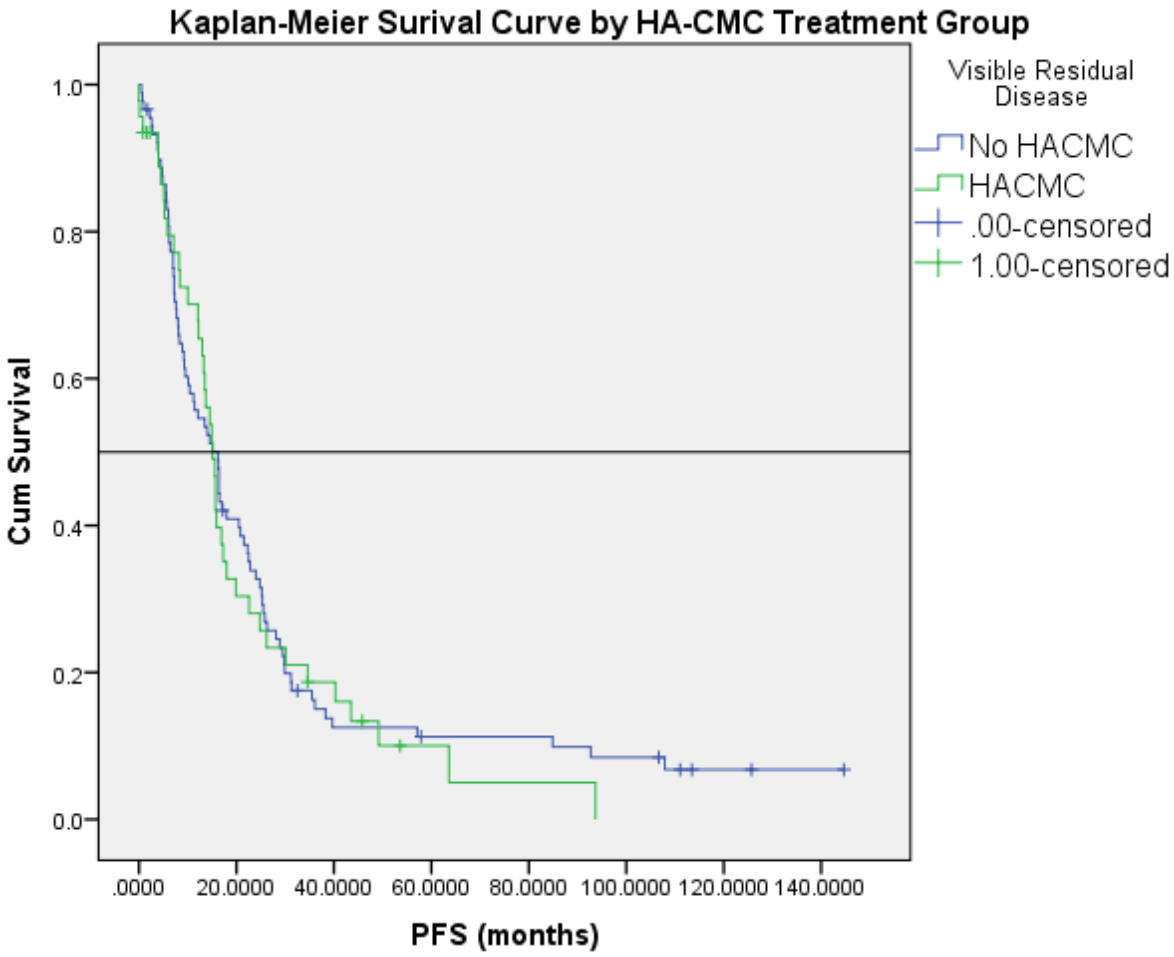

Table 1.1 Baseline Demographic and Clinical Characteristics

Patient/Tumor Characteristics	HA-CMC (n=130)		No HA-CMC (n=158)		
	No.	**%**	**No.**	**%**	**P-value†**
Age (years)					0.48
<50	32	24.6	30	18.9	
50-70	74	56.9	94	59.5	
≥ 70	24	18.5	34	21.5	
					0.39
Race					
White	110	84.6	125	79.1	
Black	11	8.5	25	15.8	
Asian	6	4.6	6	3.2	
Hispanic	2	0.6	1	1.5	
ASA					0.04*
1-2	120	92.3	130	82.3	
3-4	10	7.7	28	17.7	
Performance Status					0.02*
0	108	83.1	109	69.0	
≥ 1	22	16.9	49	31.0	
Albumin (low< 3 g/dL)	45	35.2	60	39.5	0.46
FIGO Stage					0.80
Stage III	98	75.4	117	74.1	
Stage IV	32	24.6	41	26.0	
Tumor Histology					0.67
Serous	108	83.1	135	85.4	
Non-serous	22	16.9	23	14.6	
Platinum Resistant (<6 months)	31	23.8	54	34.2	0.06
Intermediate (6-12months)	24	18.5	17	10.8	0.06
Platinum Sensitive (>12months)	66	52.0	82	52.0	0.9

HA-CMC = Sodium Hyaluronate-Carboxymethylcellulose; ASA = American Society of Anesthesiologists Classification; FIGO = International Federation of Gynecology and Obstetrics; g/dL = grams per deciliter.

† Value for treatment group frequencies analyzed using independent Fischer's exact test or Chi squared test as appropriate.

* *P* value less than 0.05.

Table 1.2 Surgical Parameters, Postoperative Outcomes, and Adjuvant Therapy according to HA-CMC use

Surgical/ Postoperative Variables	HA-CMC (n=130)		No HA-CMC (n=158)		
	No.	**%**	**No.**	**%**	**P-value†**
Debulking					
Primary	107	82.3	133	84.2	0.67
Interval	23	17.7	25	15.8	
Residual Disease (mm)					0.002*
NGRD=0	84	64.6	69	43.7	
≤ 5	15	11.5	24	15.2	
> 5-10	31	23.9	65	41.1	
Procedures					
Hysterectomy	109	83.8	120	75.9	0.2
Rectosigmoid resection	68	52.3	57	36.3	0.01*
Total omentectomy	125	96.2	148	94.3	0.46
Small bowel resection	20	12.7	13	10.0	0.56
Splenectomy	24	18.5	16	10.2	0.04*
Nodal dissection	117	90.0	106	67.5	<0.001*
Diaphragm stripping/resection	67	51.5	46	29.3	<0.001*
Liver resection	12	9.2	8	5.1	0.17
SCS Risk Category					<0.001*
Low	23	17.7	49	31.2	
Intermediate	38	29.2	73	46.5	
High	69	53.1	35	22.3	
Estimated blood loss (≥1 L)	39	30	33	21.6	0.11
Major Morbidity	43	33.1	44	28.0	0.2
IP chemotherapy	35	26.9	5	3.2	<0.001*
Disease Recurred					0.13
No	22	16.9	17	10.8	
Yes	108	83.1	141	89.2	
Dead of disease	81	62.3	124	78.5	0.003*

HA-CMC = Sodium Hyaluronate-Carboxymethylcellulose; NGRD = no gross residual disease; Major morbidity = major postoperative complications within 30 days after surgery.
† Value for treatment group frequencies analyzed using independent Fischer's exact test or Chi squared test as appropriate.
* *P* value less than 0.05.

Table 2.1 Univariate and Multivariate Survival Analysis for Progression Free Survival (N= 288)

	Univariate Analysis‡			Multivariate Model§		
Variable	**Median PFS (months)**	**95% CI**	**P value†**	**Hazard Ratio (HR)**	**95% CI**	**P value§**
HA-CMC			**0.38**			
Control	**16.4**	**14.0 – 18.8**		**1.00 (ref)**		
Exposed	**16.8**	**14.3 – 19.2**		**1.10**	**0.83 - 1.45**	**0.5**
Age (years)			0.04*			
Age < 50	19.9	12.2 - 27.7		1.00		
Age 50 -70	15.4	13.4 – 17.4		1.33	0.96 -1.86	0.09
Age ≥ 70	18.0	12.1 – 23.8		0.95	0.63 - 1.45	0.77
ASA			0.14			
1-2	16.6	13.9 -19.3		1.00		
≥ 3	15.5	14.4 – 16.6		1.18	0.75 - 1.86	0.47
PS						
0	17.2	14.7-19.7	0.07	1.00		
1-3	14.0	8.6 – 19.3		1.14	0.79 - 1.64	0.50
Stage			0.009*			
III	17.7	14.7 – 20.7		1.00		
IV	13.7	9.4-18.0		1.98	0.90 - 1.65	0.20
Debulking			0.001*			
Primary	17.2	14.8 – 19.6		1.00		
Interval	12.1	8.0 – 16.2		1.72	1.23 - 2.41	0.002*
RD			0.05*			
Visible RD	15.1	13.1 – 17.1		1.00		
NGRD	18.3	15.0 – 21.6		0.73	0.56 - 0.96	0.02*
SCS Risk Category						
Low	21.5	14.9 – 28.1	0.29	1.00		
Intermediate	15.9	14.0 – 17.9	0.86			
High	15.8	12.8 – 18.8	0.19	1.36	1.03 – 1.79	0.03*

PFS = progression free survival; HR = hazard ratio; CI = confidence interval; PS = performance status; RD = macroscopic residual disease; NGRD = no gross residual disease; SCS = surgical complexity score; ref = reference group for statistical test.
‡ Kaplan-Meier survival analysis.
† Value for univariate analysis using log-rank test; *P* <0.2 included in multivariate model.
§ Cox Proportional Hazard Model adjusted for age, comorbidity, performance status, stage, residual disease, and SCS.
* *P* value less than 0.05.

Table 2.2 Univariate and Multivariate Survival Analysis for Overall Survival (N=288)

	Univariate Analysis‡			Mutlivariate Model§		
Variable	**Median OS (months)**	**95% CI**	**P value†**	**Hazard Ratio (HR)**	**95% CI**	**P value§**
HA-CMC			**0.34**			
Control	**36.0**	**27.4 – 44.6**		**1.00**		
Exposed	**40.6**	**27.8 – 53.4**		**0.98**	**0.73 - 1.32**	**.89**
Age (years)			0.048*			
Age < 50	60.4	40.2 - 80.5		1.00 (ref)		
Age 50 -70	40.3	35.0 – 45.6		1.40	0.97 - 2.02	.076
Age ≥ 70	31.4	21.9 – 40.9		1.65	1.07 - 2.54	.02*
PS						
0	51.5	39.2 – 63.8	<0.001*	1.00		
1-3	22.9	16.9 – 28.9		1.85	1.33 - 2.56	<0.001*
Stage						
III	43.7	32.9 – 54.4	0.001*	1.00		
IV	29.2	20.3 – 38.1		1.35	0.98 - 1.88	.07
RD						
Visible RD	33.7	26.2 – 41.2	0.01*	1.00		
NGRD	50.4	37.2 – 44.5		0.71	0.53 - 0.95	.02*
Surgical Complications						
None	45.7	36.4 – 55.0	0.004*	1.00		
Major Morbidity	28.2	20.3 – 36.1		1.400	1.04 - 1.89	.03*
Platinum Resistant€ (<6 months)	19.4	15.5 – 23.3				
Platinum Sensitive (>12months)	59.4	49.2 – 69.6	<0.001*		-	- -

OS = overall survival; HR = hazard ratio; CI = confidence interval; RD = macroscopic residual disease; NGRD = no gross residual disease; ref = reference group for statistical test.

‡ Kaplan-Meier survival analysis.

† Value for univariate analysis using log-rank test; *P* <0.2 included in multivariate model.

§ Cox Proportional Hazard Model adjusted for age, comorbidity, performance status, stage, residual disease, and SCS. Parsimonious model obtained using step-wise backward elimination. € = Model no adjusted for platinum resistance.

* *P* value less than 0.05.

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APPENDIX A: SCS Measure

Surgical Complexity Scoring Guide and Risk Category Assessment

Surgical Complexity Score Criteria [25]

Procedure	**Points**
Hysterectomy/BSO	1
Omentectomy	1
Pelvic Lymphadenectomy	1
Para-aortic Lymphadenectomy	1
Pelvic peritonectomy	1
Abdominal peritoneal stripping	1
Rectosigmoid resection	3
Large Bowel Resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection	2
Small bowel resection	1

SCS/Risk Category	**Total Points**
Low/Simple	3 or fewer
Intermediate	4-7
High/Complex	8 or more

SCS = surgical complexity score; BSO = bilateral salpingo-oophorectomy.

APPENDIX B: Measures of Medical Comorbidity and Functional Capacity

American Society of Anesthesiologists (ASA) Physical Status Classification System [26]

ASA	Category	Description
1	Normal healthy patient	No organic, physiologic, or psychiatric disturbance; healthy with good exercise tolerance
2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
5	Moribund patients who are not expected to survive without the operation	Not expected to survive > 24 hours without surgery; imminent risk of death; multi-organ failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy

COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure.

ECOG Performance Status (PS) Scale [27]

PS	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group; PS = performance status.