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Neoadjuvant Chemotherapy Versus Primary Cytoreductive Surgery for Stage IV Uterine Serous Carcinoma

Ivy Wilkinson-Ryan, MD^{*,a}, Antonina I. Frolova, MD, PhD^a, Jingxia Liu, PhD^b, L. Stewart Massad, MD^a, Premal H. Thaker, MD^a, Matthew A. Powell, MD^a, David G. Mutch, MD^a, and Andrea R. Hagemann, MD^a

^aDepartment of Obstetrics and Gynecology, Division of Gynecologic Oncology, Campus Box 8064

^bDivision of Biostatistics, Campus Box 8064, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110, USA

Abstract

Objective—This study compares surgical and survival outcomes of women with stage IV uterine serous carcinoma (USC) treated with neoadjuvant chemotherapy (NAC) and interval cytoreduction to women treated with primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy.

Methods—This retrospective dual cohort study included women diagnosed with stage IV USC at a single academic institution. Kruskal-Wallis and Fisher's exact tests were used to compare demographics and surgical outcomes. Progression-free (PFS) and overall survival (OS) was estimated by using Kaplan-Meier methods. Comparison between study groups was tested by log-rank statistics.

Results—Ten women with stage IV USC who received NAC and 34 who underwent PCS met inclusion criteria. NAC patients had a lower mean BMI and were more often African American. Compared to PCS, the NAC cohort had shorter mean operative times (137±66 minutes versus 203±80 minutes, $P=0.025$) and were discharged from the hospital earlier (median length of stay 3 vs. 5 days, $P=0.002$). Rates of debulking to no gross residual disease (70% NAC v. 32.3% PCS) or <1cm of disease (30% NAC v. 50% PCS) did not differ ($p=0.10$). Median follow-up time was 17.5 months. There was no difference in median PFS (10.4 v. 12 months, $p=0.29$) or OS (17.3 v. 20.7 months, $p=0.23$) for NAC and PCS cohorts.

Conclusions—Women receiving NAC for Stage IV USC had shorter surgeries and hospital stays than those receiving PCS. There was no difference in PFS or OS, although our sample size was small. NAC may be an appropriate therapy for select patients with advanced stage USC.

Keywords

Uterine serous carcinoma; neoadjuvant chemotherapy; endometrial carcinoma

*Corresponding Author: Ivy Wilkinson-Ryan, 4911 Barnes-Jewish Hospital Plaza, Campus Box 8064, St. Louis, MO 63110, ivywilkr@gmail.com, phone: 215-713-4785, fax: 314-362-2893.

Introduction

Uterine serous carcinoma (USC) accounts for only 10% of uterine cancers but is associated with a significantly poorer prognosis than the more common endometrioid-type uterine cancers^(1, 2); the overall five-year survival rates are 55% and 77%, respectively⁽¹⁾. Although limited data exists to guide treatment, optimal surgical cytoreduction is highly correlated with prolonged survival^(3–6). Women with stage III–IV USC have a median survival of 9.6–14 months after suboptimal cytoreduction and 26.2–51 months after optimal cytoreduction^(3, 5, 6). Adjuvant treatment with platinum and taxane-based chemotherapy in addition to radiation therapy has also been shown to improve progression-free and overall survival^(6–10).

USC frequently metastasizes and requires aggressive cytoreductive surgery for optimal treatment, much like ovarian cancer^(1, 7). Currently, management of USC includes primary cytoreduction surgery (PCS) followed by adjuvant chemotherapy with or without radiation^(11, 12), with primary chemotherapy typically reserved for patients too sick to undergo surgery. In 2010, a randomized trial in advanced-stage ovarian cancer reported that neoadjuvant chemotherapy (NAC) followed by interval cytoreduction was not inferior to primary cytoreduction surgery followed by chemotherapy⁽¹³⁾. Since this finding, NAC has been increasingly used in ovarian cancer. Despite the similarities between ovarian cancer and USC, NAC is not standard treatment for women with USC, although it has occasionally been used for women with high tumor burden or comorbidities that prohibit primary surgery^(14–16).

Few studies have evaluated the effectiveness of NAC in USC. In the largest series, Vandenput et al. followed 27 USC patients treated with NAC and found that their outcomes were comparable to published survival data for women treated with PCS (progression-free survival of 13 months and overall survival of 23 months)⁽¹⁷⁾. Limited data indicate that, although it may not change survival, NAC may increase time out of the hospital and decrease perioperative morbidity in women with advanced-stage USC^(13, 17). The goal of this study was to compare surgical and survival outcomes for women with USC treated with NAC and interval cytoreduction versus women who underwent PCS followed by adjuvant chemotherapy.

Methods

This retrospective dual cohort study was undertaken at a single academic institution and approved by the Human Studies Committee at Washington University. Women were included if they were over the age of 18, had stage IV disease with papillary serous histology or mixed histology with >50% papillary serous component, and underwent surgical tumor cytoreduction between January 1, 2000 and June 30, 2013. Eligible subjects were identified from a surgical database maintained within the division of gynecologic oncology. Women were excluded from this analysis if they were treated with chemotherapy alone and did not undergo cytoreductive surgery. At our institution, neoadjuvant chemotherapy was offered to patients at the discretion of the treating physician.

Data about demographics, surgery, complications, pathologic findings, and hospital course were extracted from patients' electronic medical records. The Charlson comorbidity index was used to compare preexisting comorbid conditions between cohorts^(18, 19). Optimal cytoreduction was defined as no single area of disease with diameter over one cm at the conclusion of surgery. No gross residual disease was defined as no identifiable disease at the conclusion of surgery. Operative complications included wound infection, readmission or reoperation within 30 days of surgery, thromboembolism, and death. Wound complications included any process (infection, seroma, hematoma) that resulted in wound opening or treatment with antibiotics. Treatment response to therapy was established based on imaging and CA-125 levels. Progression-free intervals were calculated by radiologic (by RECIST 1.1 criteria) or pathologic evidence of recurrent disease.

Kruskal-Wallis and Fisher's exact tests were used to compare demographics and surgical outcomes. The Kaplan-Meier method was used to estimate progression-free and overall survival. Study groups were compared by log-rank statistics. All tests used a two-tailed significance level of $P < 0.05$. A sensitivity analysis for survival was performed by using a propensity-score approach. The propensity score was estimated by age, race, and comorbidities. Matched pairs were identified by using a caliper technique with a standard deviation defined as 0.125 of the estimated propensity score for NAC and PCS patients. Data were collected with RedCap software version 5.6.3 (Vanderbilt University, TN) and analyzed with SAS version 9.3 (SAS institute, NC).

Results

Thirty-four women treated with PCS and 10 women treated with NAC prior to interval cytoreductive surgery met our inclusion criteria. Median age for the entire cohort was 70.5 years (range, 37 – 91). Women who received NAC were more likely to be African American and had a lower mean BMI, but were otherwise similar to women treated with PCS. There were no differences in comorbidity scores or performance status (Table 1).

Surgical outcomes are compared in Table 2. Women treated with NAC had shorter mean operative times (137 ± 66 minutes versus 203 ± 80 minutes, $p=0.025$). Seventy percent of NAC patients had no gross residual disease and the remaining 30% had visible disease < 1 cm, whereas 32.3% of PCS patients had no gross residual disease at the conclusion of their cytoreductive surgery and 50% had visible disease < 1 cm ($p=0.10$). Complication rates were not significantly different between the two groups ($p=0.13$). However, in the primary cytoreduction group there were more cumulative complications: 16 total complications among 13 patients, including VTE ($n=4$), wound complications ($n=5$), readmission ($n=5$), and death ($n=2$) versus one wound complication in the NAC arm. One of the patients in the PCS cohort died of acute respiratory distress syndrome following surgery, and another patient died of cardiac arrest. Patients who underwent NAC had shorter hospital stays after their interval cytoreductive surgery (median 3 days (range 2 - 8) versus 5 days (range 3 - 31), $p=0.002$).

All patients receiving NAC were treated with taxane and platinum agents. One patient was treated with triplicate therapy with the addition of doxorubicin. Four patients received three

cycles of chemotherapy, two patients received four cycles, and four patients received six-to-eight cycles of chemotherapy prior to their interval cytoreductive surgery. Nine of the 10 NAC patients responded to chemotherapy, as judged by CA-125 values; there was an average decline of $91 \pm 11\%$ from the time of diagnosis to the completion of NAC. The median CA-125 at the time of diagnosis was 347 Units/mL in the NAC cohort and 250 Units/mL in the PCS cohort. Whereas all ten patients in the NAC cohort had an elevated CA-125 at the time of diagnosis, three of the 34 women undergoing PCS had normal CA-125 levels at the time of diagnosis. During NAC, two patients (20%) experienced grade 1–2 neuropathy, and one patient (10%) was treated with growth factors and antibiotics for neutropenic fever. Table 3 describes the clinical scenarios of each patient who underwent NAC.

In the PCS cohort, patients received a median of six cycles of adjuvant chemotherapy (range, 0 – 13). Four patients (11.8%) were treated for neutropenic fever, six women (17.6%) had chemotherapy-induced anemia requiring transfusion and/or treatment delay, and 10 (29.4%) women experienced neuropathy from chemotherapy (nine had grade 1 - 2 neuropathy and one had grade 3 neuropathy). One NAC patient declined adjuvant therapy. The nine patients in the NAC cohort who underwent adjuvant chemotherapy received a median of three cycles of adjuvant chemotherapy (range, 2 – 12). In the NAC cohort, three patients (30%) were treated for neutropenic fever during post-cytoreduction adjuvant therapy. Another two patients (20%) developed thrombocytopenia requiring dose delay, and two (20%) developed anemia requiring transfusion or treatment delay during post-operative chemotherapy. There was no difference in response to therapy at the conclusion of treatment between the NAC and PCS groups (80% and 92.5% reduction in CA-125 levels, respectively; $P=0.43$). Ten women (29.4%) in the PCS cohort underwent adjuvant radiation. One patient in the NAC group underwent neoadjuvant radiation, but no patients in this group received radiation post-operatively.

Median follow-up time for all patients is 17.5 months. Seven patients (70%) in the NAC cohort recurred and died of their disease within the follow up period. In the PCS cohort, 22 patients (64.7%) have experienced a recurrence, 20 patients (58.8%) died of their disease, and nine patients died of other causes. There was no difference in median progression-free survival (10.4 versus 12.0 months; Figure 1a) or overall survival (17.3 versus 20.7 months; Figure 1b) between the NAC and PCS groups. These findings were consistent with those from sensitivity analysis using pair matching (data not shown).

Discussion

NAC has been used to effectively treat women with advanced stage ovarian cancer who are poor surgical candidates, thereby sparing them the potential high morbidity and low yield associated with suboptimal primary debulking surgery⁽¹³⁾. USC has similar tumor biology to ovarian cancer and carries a similarly poor prognosis^(3, 5–7, 20). Although advanced stage USC is sensitive to taxane and platinum agents with 70–90% of patients responding to chemotherapy, disease free survival is limited (6–18 months) in patients who undergo optimal treatment with surgical resection and adjuvant therapy^(6, 21, 22). In this series, we evaluated the surgical and survival outcomes for two groups of women with USC: those

treated with NAC before interval cytoreductive surgery and those treated with PCS and adjuvant therapy. There were no significant differences in performance status or comorbidity scores between the NAC and PCS cohorts. Women treated with NAC were more likely to have no gross residual disease and had fewer post-op complications than those treated with PCS, but these differences were not statistically significant. There was no difference in survival between the two cohorts, but our study was not powered to detect this. The significant findings from our study were that women treated with NAC had shorter surgeries and shorter postoperative hospital stays than women treated with PCS.

In addition to the limitations inherent to retrospective studies, this study is limited by small sample size, single institution experience, and short follow-up time. With larger numbers and longer follow-up times, differences might emerge in the progression-free and overall survival between the two cohorts. Presumably, patients with advanced-stage USC who are treated with NAC have either a poor performance status or aggressive disease, both of which negatively affect survival. We detected no difference in performance status between the two groups, suggesting that the decision to treat with NAC was largely based on tumor burden. The lack of differences in performance status and comorbidities was potentially due to the exclusion of patients who were unable to undergo cytoreductive surgery at any point, a group likely to have a poor performance status. Patients received three to eight cycles of NAC; because of this wide range, we were unable to draw any conclusions about the ideal number of preoperative cycles of chemotherapy. Despite this heterogeneity within our NAC cohort, we were able to identify advantages in surgical outcomes.

In a retrospective study of 31 women with stage IV USC, Bristow et al. described a 17-month survival advantage for women who were able to be optimally cytoreduced at their primary debulking surgery ⁽³⁾. Similar results were seen by Thomas et al. in a review of women with stage III-IV USC ⁽⁵⁾. These findings suggest that, similar to ovarian cancer, optimal debulking may be one of the most influential modifiable factors affecting prognosis. Ours is the first study comparing outcomes between women with USC treated with NAC and those treated with PCS. In this pilot study, we identified significant differences in operative time and day of discharge in favor of NAC without appearing to significantly worsen prognosis. Because selection of patients was based largely on tumor burden, it is likely that the NAC cohort was biased towards more aggressive disease. We conclude that in this highly morbid disease, consideration should be given to treatment that decreases length of hospitalization and perioperative morbidity. Future studies, including the formation of a cross-institutional registry, could help identify preoperative characteristics to determine which women will benefit most from NAC.

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Figure 1.

Figure 1A - Progression free survival

Figure 1B - Overall Survival

Table 1

Patient demographics and tumor characteristics

	Neoadjuvant Chemotherapy n=10	Primary Cytoreductive Surgery n=34	P-value ^[1]
Age – mean (SD) ^[2]	65.2 (14.3)	69.6 (10.3)	0.39
Race – n (%)			0.034
Non-Hispanic white	3 (30)	23 (69.7)	
African American	7 (70)	10 (30.3)	
BMI – mean (SD)	26.9 (5.6)	31.6 (7.8)	0.042
Comorbidities – n (%)			
CAD ^[3]	0	7 (20.6)	
COPD ^[4]	0	2 (5.9)	
DVT/PE/VTE ^[5]	1 (10)	0	
Diabetes	1 (10)	6 (17.6)	
Charlson Index – n (%)			0.20
0	1 (10.0)	0	
1	1 (10.0)	1 (2.9)	
2	0	2 (5.9)	
3	8 (80.0)	31 (91.2)	
GOG performance status – n (%)			0.69
0	8 (80)	27 (79.4)	
1	1 (10)	5 (14.7)	
2	1 (10)	1 (2.9)	
3	0	1 (2.9)	
Histology - n (%)			1.0
USC	6 (60)	20 (58.8)	
USC/Endometrioid	3 (30)	9 (26.5)	
USC/Clear cell	1 (10)	3 (8.8)	
USC/Endometrioid/Clear cell	0	2 (5.9)	

^[1] 2-sided Kruskal-Wallis or Fisher's exact test^[2] Standard deviation^[3] Coronary artery disease^[4] Chronic obstructive pulmonary disease^[5] Deep venous thrombosis/pulmonary embolism/venous thromboembolism

Table 2**Surgical outcomes**

	Neoadjuvant Chemotherapy n=10	Primary Cytoreductive Surgery n=34	P-value^[1]
Operative time, min – mean (SD)	136.9 (65.5)	202.6 (79.9)	0.025
Estimated blood loss, mL – mean (SD)	410 (334.8)	781.8 (781)	0.063
Post op complications – n (%)	1 (10)	13 (38.2)	0.13
Wound complication	1 (10)	5 (14.7)	
PE/DVT/VTE	0	4 (11.8)	
Readmission	0	5 (14.7)	
Death	0	2 (5.9)	
Debulking – n (%)			0.10
Suboptimal (>1 cm)	0	6 (17.7)	
Optimal (≤ 1 cm)	3 (30.0)	17 (50.0)	
No gross residual	7 (70.0)	11 (32.3)	
Days of hospital stay – median (range)	3 (2–8)	5 (3–31)	0.0021

^[1] 2-sided Kruskal-Wallis or Fisher's exact test

Table 3

NAC cohort characteristics

Case #	Histology	Chemotherapy regimen	# Cycles	Pre-NAC CA-125	Post-NAC CA-125	GOG ^{1/1} Performance Status	Reason for Neoadjuvant Chemotherapy
1	USC	Carboplatin, Paclitaxel	6	1877	11	0	CT findings of innumerable axillary and mediastinal LAD ² , lesions in liver and spleen. Chemotherapy course extended from 4 to 6 cycles because of motor vehicle accident delaying surgery.
2	USC	Doxorubicin, Cisplatin, Paclitaxel	3	186	14	0	CT findings of widespread disease with metastases to the omentum cervix and vagina. Also abdominal and pelvic LAD.
3	USC/Endometrioid	Carboplatin, Taxotere	8	354	23	0	CT findings of multiple pulmonary nodules, diffuse mesenteric and pelvic LAD, ascites.
4	USC/Endometrioid	Carboplatin, Paclitaxel	4	101	9	0	Diagnostic laparoscopy revealed significant adhesions and scarred tissue planes secondary to cancer.
5	USC	Carboplatin, Paclitaxel	3	2200	297	2	CT findings of omental caking, liver and pulmonary nodules.
6	USC/Clear cell	Carboplatin, Paclitaxel,	6	154	55	0	First-look surgery revealed extensive carcinomatosis that prevented identification of bladder, uterus or ovaries.
7	USC	Carboplatin, Paclitaxel	4	206	277	0	CT findings of ascites, pleural effusion, pelvic mass. Pulmonary nodules noted on video-assisted thorascopic surgery.
8	USC/Endometrioid	Carboplatin, Paclitaxel	6	3999	17	1	CT findings of large uterine mass and diffuse LAD, including retroperitoneal, omental, mesenteric, inguinal, and axillary.
9	USC	Carboplatin, Dose-dense Paclitaxel	3	3972	59	0	CT findings of large pleural effusion, omental caking, and peritoneal carcinomatosis.
10	USC	Carboplatin, Paclitaxel	3	339	20	0	CT findings of large pelvic mass, favoring uterine versus ovarian origin, extensive peritoneal and omental carcinomatosis, pelvic and retroperitoneal LAD.

^{1/1} Gynecologic oncology group