

Original Article



Evaluation of the optimal sequence of adjuvant chemotherapy and radiation therapy in the treatment of advanced endometrial cancer

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ABSTRACT

Objective: The optimal sequence of adjuvant chemoradiation in the treatment of advanced endometrial carcinoma (EC) remains unclear. We sought to evaluate the outcomes of patients treated with chemoradiation in sandwich fashion (chemotherapy-radiotherapy-chemotherapy; CRC), versus those treated sequentially (chemotherapy-radiotherapy; CR) (radiotherapy-chemotherapy; RC), to determine if there is a survival advantage associated with a particular treatment sequence.

Methods: A multicenter retrospective analysis of patients with stage III and IV EC from 2000-2018 was conducted. Inclusion criteria were patients who had undergone comprehensive surgical staging/tumor debulking; followed by adjuvant chemoradiation. Differences in the frequencies of adverse events were evaluated using Pearson's χ^2 test. Progression free survival (PFS) and overall survival (OS) rates were calculated using Kaplan-Meier estimates.

Results: Final analysis included 152 patients; 36.8% (n=56) CRC, 28.9% (n=44) CR, and 34.2% (n=52) RC. Histology included 44.0% endometrioid, 47.5% serous and 8.5% clear cell tumors. There was no difference in the frequency of histology (p=0.973), stage (p=0.143), cytoreduction status (p=0.932), or treatment delays (p=0.571) between adjuvant therapy sequences. The most frequent location of disease recurrence was abdomen. The median PFS favored CRC versus CR or RC (36-months vs. 22-months and 24-months, respectively) (p=0.038), as did the median OS (48-months vs. 28-months and 34-months, respectively) (p=0.003). CRC demonstrated superiority over CR and RC sequencing in terms 3-year PFS (55% vs. 34% and 37%, respectively) and 3-year OS (71% vs. 50% and 52%, respectively).

Conclusions: Adjuvant chemoradiation delivered in CRC sequence was associated with improvements in both PFS and OS compared to alternant therapy sequencing.

Keywords: Endometrial Carcinoma; Radiotherapy; Chemotherapy

INTRODUCTION

Endometrial carcinoma (EC) represents the most common gynecologic malignancy. It is estimated that there will be 65,620 new cases in 2020 [1]. Its incidence is increasing particularly in the United States, Western Europe and Canada. This is in part due to an aging

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Presentation

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Author Contributions

Conceptualization: M.J., S.P., L.Y.C.; Data curation: Z.N., S.C., S.L., C.C.; Formal analysis: M.J.; Methodology: M.J., L.Y.C.; Project administration: L.Y.C.; Writing - original draft: M.J.; Writing - review & editing: Z.N., S.P., L.Y.C.

population, however, the increase in obesity and metabolic syndrome in these developed regions is an important contributing factor [2]. The majority of EC is diagnosed at early stage with an overall good prognosis. However, 20% of patients will present with locally advanced disease (FIGO stage IIIA-IVA) and another 8% of patients will present with distant metastatic disease (FIGO stage IVB) [3,4]. Despite excellent outcomes in early stage disease, the 5-year survival declines dramatically at advanced stages, falling to a dismal 0%–18% in stage IV [5-9].

Patients with extrauterine disease are at increased risk of recurrence, metastatic spread and subsequently lower survival. Systemic chemotherapy has been shown to improve survival in advanced disease and is the backbone of therapy in this patient population. However, chemotherapy alone has been associated with an increase in local recurrence, with pelvic relapse rates ranging from 18%–40% [10-12]. Additionally, chemotherapy alone rarely affords long-term disease-free survival. The prospective randomized trial conducted by the Gynecologic Oncology Group (GOG) 209, established carboplatin-paclitaxel as the first-line systemic therapy regimen for the treatment of advanced EC. However, more than a decade later, we have observed little progress in improving this regimen, which sports a median progression free survival (PFS) of only 14 months [5]. These findings emphasize inadequacy of systemic chemotherapy alone in the treatment of advanced EC, and the need for better therapeutic regimens.

Several authors have reported combination adjuvant therapy with both systemic chemotherapy and radiation produces superior clinical outcomes compared to either modality alone [13-17]. Secord et al. [13] demonstrated improved PFS and overall survival (OS) in those patients treated with adjuvant chemoradiation compared to those treated with either modality alone. Similarly, Goodman et al. compared the outcomes of patients with stage III/IVA disease treated with a chemoradiation to that of either modality alone and observed improved outcomes in the combination therapy cohort [16]. More recently, Albeesh et al. [15] observed improved OS in patients treated with a combination of chemoradiation versus external beam radiation therapy (EBRT) alone. Despite a wealth of evidence supporting multimodality therapy, there is no consensus on the optimal sequence of chemoradiation in this patient population. “Sandwich” sequencing of chemoradiation has been evaluated by several authors. In this setting, the patient receives 3 cycles of chemotherapy, followed by EBRT+/- vaginal brachytherapy, followed by an additional 3 cycles of chemotherapy. The sandwich sequence has been associated with improved PFS and OS, as well as favorable toxicity profile compared to alternate sequences of therapy [18-24]. Current literature supporting sandwich sequencing is limited by the heterogeneity and small sample size. Nevertheless, our institution, as well as others, has administered multimodality therapy in a sandwich fashion based on these positive results. In the present study, we review our experience with “sandwich” sequencing (chemotherapy-radiotherapy-chemotherapy; CRC) in comparison to chemoradiation delivered alternate sequences, chemotherapy followed by radiotherapy (CR) and radiotherapy followed by chemotherapy (RC), to determine the optimal sequence of adjuvant therapy in advanced EC.

MATERIALS AND METHODS

From 2000–2018, a multicenter retrospective analysis of patients with advanced EC was conducted. Participating institutions included SUNY Downstate Medical Center–Health Science University, King's County Hospital Center and Good Samaritan Hospital Medical Center. Internal Review Board (IRB) approval was obtained at all participating sites.

Tumor registries were reviewed to identify all patients with advanced EC who received primary surgical treatment, followed by adjuvant therapy with both chemotherapy and radiotherapy. Inclusion criteria were patients with a diagnosis of advanced EC who had undergone primary surgical management, consisting of hysterectomy with or without bilateral salpingoophorectomy, surgical staging and/or tumor debulking, followed by adjuvant chemoradiation. Surgical staging was defined as pelvic +/- paraaortic lymph node dissection +/- omentectomy. Tumor debulking was defined as removal of extra-uterine gross tumor from the abdominopelvic cavity. Advanced EC was defined as stage III–IV disease. Key exclusion criteria included histologic diagnosis of carcinosarcoma or other sarcoma, patients with incomplete surgical staging, patient receiving neoadjuvant chemotherapy and/or preoperative pelvic radiation and patients receiving chemotherapy or radiotherapy alone.

Clinical and demographic data were obtained from a review of the tumor registry, operative notes, pathology reports and both inpatient and outpatient medical records. Data regarding date of diagnosis, surgical procedures, cytoreduction status, types of adjuvant therapy, date and site of recurrent, chemotherapy regimen, number of chemotherapy cycle received, type of radiation therapy received, treatment delays, adverse events and date of death were extracted. Optimal cytoreduction was defined as total residual tumor less than or equal to 1 cm in diameter and suboptimal debulking was defined as tumor amounting to greater than 1 cm of disease. At all participating institutions, patients were monitored for disease recurrence with routine history and physical exam every 3 months after completion of adjuvant therapy. Imaging was obtained at the completion of initial prescribed adjuvant therapy if there was suspicion for disease recurrence based on physical examination findings or symptoms. Imaging modalities used to diagnose recurrence included computed tomography (CT) scan of the chest, abdomen and pelvis or positron emission tomography (PET)-CT scan. A one-way analysis of variance test was used to compare differences in mean age between treatment arms. Differences in the frequencies of stage, cytoreduction status, treatment delays and sites of disease recurrence were identified using Pearson's χ^2 test. PFS was defined as the time of surgery to the time of first recurrence. OS was defined as time of surgery to time of death. Patients who were alive at date of last follow up were censored. PFS and OS rates were calculated using Kaplan-Meier estimates. Statistical significance was defined as $p < 0.05$. Analysis was performed using SPSS version 25.0 (IBM, Armonk, New York).

RESULTS

1. Patient characteristics

Final analysis included 152 patients receiving dual modality postoperative adjuvant therapies. Fifty-six (36.8%) received CRC, 44 (28.9%) received CR, and 52 (34.2%) received RC. The median age was 65 years (range 50–87) and the majority of patients in all cohorts were African-American (80%). Histology included 44.0% endometrioid, 47.5% serous and 8.5% clear cell carcinomas. Stage distribution included 80% stage III and 20% stage IV. 95% of patients underwent optimal cytoreduction. There was no difference in the frequency of different histologic subtypes ($p=0.973$), stage ($p=0.143$), cytoreduction status ($p=0.932$), or treatment delays ($p=0.571$) between the various adjuvant therapy sequences (**Table 1**).

2. Adjuvant therapy

The majority of patients received platinum-based chemotherapy (98.7%). The most common regimen was carboplatin-paclitaxel (83.6%). Other regimens included cisplatin paclitaxel

Chemoradiation sequence in advanced endometrial carcinoma

Table 1. Clinical and pathologic characteristics

Characteristics	All patients (n=152)	CRC (n=56)	CR (n=44)	RC (n=52)	p-value
Age at surgery	65 (47–85)	66.0 (48–81)	65.6 (48–83)	64.9 (47–85)	0.786
Race					0.861
Caucasian	27 (18)	11 (20)	6 (14)	10 (19)	
African-American	121 (80)	44 (79)	37 (84)	40 (78)	
Other	4 (2)	1 (1)	1 (2)	2 (3)	
Histologic type					0.973
Endometrioid					
G1	12 (8)	6 (11)	2 (5)	4 (8)	
G2	23 (15)	9 (16)	6 (14)	8 (15)	
G3	40 (26)	14 (25)	12 (27)	14 (27)	
Serous	63 (41)	22 (39)	20 (45)	21 (40)	
Clear cell	14 (10)	5 (9)	4 (9)	5 (10)	
FIGO stage					0.143
IIIA	5 (3)	2 (4)	1 (2)	2 (4)	
IIIB	6 (4)	2 (4)	1 (2)	3 (5)	
IIIC1	69 (45)	25 (44)	17 (39)	27 (52)	
IIIC2	42 (27)	15 (26)	13 (29)	14 (27)	
IVA	1 (1)	0 (0)	0 (0)	1 (2)	
IVB	29 (19)	12 (22)	12 (28)	5 (10)	
Cytoreduction status					0.932
Optimal	145 (95)	53 (95)	42 (95)	50 (96)	
Suboptimal	7 (5)	3 (5)	2 (5)	2 (4)	
Chemotherapy regimen					-
Carboplatin-paclitaxel	127 (84)	48 (85)	35 (80)	44 (84)	
TAP	16 (10)	6 (11)	5 (11)	5 (10)	
AP	4 (3)	2 (4)	1 (2)	1 (2)	
Cisplatin-paclitaxel	3 (2)	0 (0)	2 (5)	1 (2)	
Doxorubicin	2 (1)	0 (0)	1 (2)	1 (2)	
EBRT dose (cGy)	5,245 (4,050–7,020)	5,210 (4,050–7,020)	5,149 (4,050–6,800)	5,400 (4,050–7,020)	-
VBT dose (cGy)	1,343 (900–2,100)	1,435 (1,050–2,100)	1,380 (1,150–1,800)	1,340 (900–2,100)	-

Values are presented as mean (range) or number (%).

AP, cisplatin-adriamycin; CRC, chemotherapy-radiotherapy-chemotherapy; CR, chemotherapy followed by radiotherapy; EBRT, external beam radiation therapy; RC, radiotherapy followed by chemotherapy; TAP, cisplatin-paclitaxel-adriamycin; VBT, vaginal brachytherapy.

doxorubicin (10.5%), cisplatin-doxorubicin (2.6%), cisplatin-paclitaxel (2.0%) and single-agent doxorubicin (1.3%). There was no significant difference in treatment regimens between adjuvant therapy arms ($p=0.992$). The median number of cycles received was 6 (range 4–8). The majority of patients received EBRT to the pelvis plus vaginal brachytherapy with or without extended para-aortic field (60.5%). The remaining received a combination of EBRT +/- extended field without brachytherapy (39.5%). The mean dose of EBRT received was 5245 cGy (range: 4,050–7,020 cGy) and the mean dose of vaginal brachytherapy received was 1,343 cGy (range: 900–2,100 cGy). Fifty (32.9%) patients experienced a delay in treatment; 17 (30.4%) of CRC, 13 (29.5%) of CR and 20 (38.5%) of RC. The most common reason for treatment delay in all arms was neutropenia. There was no difference in the frequency of treatment delays between adjuvant therapy regimens ($p=0.571$) (Table 2).

3. Treatment outcomes

The median follow-up of the entire cohort was 5.5-years. The median follow-up of the CRC cohort was 4.7-years and the median follow-up the CR and RC cohorts was 5.8-years. There was a total of 88 recurrences during the study period and 120 individual sites of disease recurrence. The most frequent location of disease recurrence was the abdomen (61%), followed by the pelvis (26%), retroperitoneum (11%) and extra-peritoneal distant sites (2%). The distribution of recurrence did not differ between cohorts ($p=0.378$) (Table 3). There was a significant improvement in both PFS and OS in those patients receiving CRC. The median

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Table 2. Chemotherapy related treatment delays

Adverse event leading to treatment delay	CRC (n=56)	CR (n=44)	RC (n=52)
Neutropenia	8 (47.1)	7 (53.8)	10 (50.0)
Anemia	4 (23.5)	3 (23.1)	5 (25.0)
Thrombocytopenia	1 (5.9)	1 (7.7)	2 (10.0)
Constitutional	1 (5.9)	2 (15.4)	1 (5.0)
Neurotoxicity	2 (11.8)	0 (0.0)	1 (5.0)
Nephrotoxicity	1 (5.9)	0 (0.0)	1 (5.0)
Total	17 (30.4)	13 (29.5)	20 (38.5)

Values are presented as number (%).

CRC, chemotherapy-radiotherapy-chemotherapy; CR, chemotherapy followed by radiotherapy; RC, radiotherapy followed by chemotherapy.

Table 3. Recurrence site based on sequence of adjuvant therapy

Variables	CRC	CR	RC	All
Total number of recurrences	26	29	33	88
Total number of recurrences sites*	39	37	44	120
Recurrence site				
Abdominal	22 (56.4)	23 (62.2)	28 (63.6)	73 (60.8)
Pelvic	11 (28.2)	7 (18.9)	13 (29.5)	31 (25.8)
Retroperitoneum	3 (7.7)	7 (18.9)	3 (6.8)	13 (10.8)
Extra-abdominopelvic	3 (7.7)	0 (0.0)	0 (0)	3 (2.5)

Values are presented as number (%).

CRC, chemotherapy-radiotherapy-chemotherapy; CR, chemotherapy followed by radiotherapy; RC, radiotherapy followed by chemotherapy.

*Many patients recurred at more than one location concurrently, the above numbers reflect each individual site of recurrence. Therefore, the total number of recurrence sites far exceeds the total number of recurrences in the population.

PFS favored the CRC compared to CR and RC; 36 months vs. 22 months and 24 months, respectively (p=0.038). The median OS also favored the CRC sequence compared to CR and RC; 48 months vs. 28 months and 34 months, respectively (p=0.003) (**Fig. 1** and **Table 4**). This translated to a significant 3-year PFS benefit in the CRC cohort (54%) compared to both CR (34%) and RC (37%). Similarly, we observed a 3-year OS benefit with the use of CRC (71%) compared to alternate sequencing (CR 50% and RC 52%).

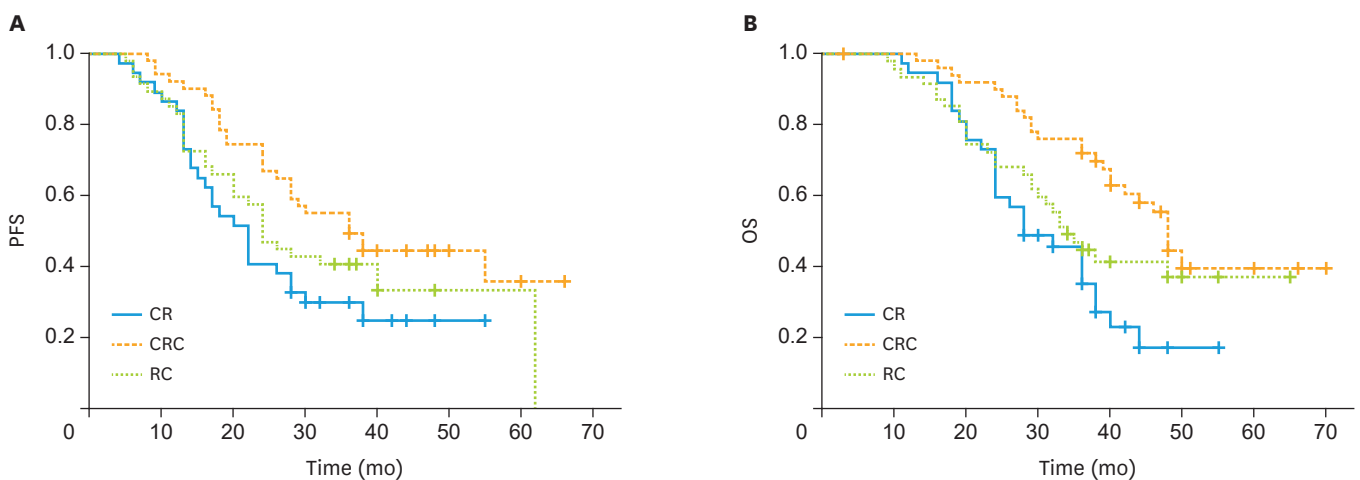


Fig. 1. Kaplan-Meier survival analysis by treatment group. (A) PFS analysis and (B) OS analysis.

CRC, chemotherapy-radiotherapy-chemotherapy; CR, chemotherapy followed by radiotherapy; RC, radiotherapy followed by chemotherapy.

Table 4. Median survival by treatment regimen

Survival	CRC	CR	RC	p
Median PFS (mo)	36	22	24	0.038
Median OS (mo)	48	28	34	0.003

CRC, chemotherapy-radiotherapy-chemotherapy; CR, chemotherapy followed by radiotherapy; RC, radiotherapy followed by chemotherapy; PFS, progression free survival; OS, overall survival.

DISCUSSION

The GOG 122 demonstrated combination chemotherapy with doxorubicin-cisplatin significantly improved PFS and OS when compared with whole-abdominal radiotherapy, establishing the superiority of chemotherapy over radiotherapy in the treatment of advanced EC [10]. From that juncture on, chemotherapy became the backbone of adjuvant therapy in this patient population and future research focused on optimization of systemic therapy regimens [5,6,10,11]. However, when chemotherapy is administered without radiation, local recurrence ranges from 18%–40% [10-12]. Earlier local recurrence contributes to symptom burden, development of retroperitoneal and distant metastatic disease, and ultimately shorter survival. Multiple retrospective reviews evaluated combination chemoradiation and reported improved outcomes with multimodality therapy. Secord et al. [13] and Goodman et al. [16] observed improved outcomes in patients with locally advanced EC treated with combination chemoradiation versus either modality alone. Similarly, Albeesh et al. [15] observed improved survival in patients treated with a chemoradiation compared to EBRT alone. These findings have led to the decision by many to utilize combination therapy rather than chemotherapy or radiotherapy alone, despite the lack of prospective data demonstrating a survival advantage with the addition of radiation to chemotherapy.

Two recent prospective randomized trials, the PORTEC-3 and GOG 258, addressed the questions of concurrent chemoradiation followed by additional systemic chemotherapy [11,25]. The experimental arm in each of these trials consisted of EBRT with concurrent cisplatin chemosensitization, followed by 4 additional cycles of carboplatin-paclitaxel. This arm was compared to EBRT alone in the PORTEC-3 or 6 cycles of carboplatin-paclitaxel in the GOG 258. The PORTEC 3 included patients with high-risk stage I–III disease. Although there was no significant difference in outcomes between the two treatment arms in the intention-to-treat population, subanalysis demonstrated improved PFS in stage III patients receiving the combination of chemoradiation versus radiation therapy alone. These findings support combination therapy in locally advanced disease, and leaving EBRT alone as the mainstay of adjuvant therapy for early stage disease [25].

The recently published GOG 258 failed to demonstrate a recurrence free survival benefit with the combination of chemoradiation versus chemotherapy alone. The combination of chemoradiation was associated with a decrease in pelvic and vaginal recurrence at the expense of increase distant metastasis compared to chemotherapy alone [11]. As a result of these two trials, there has been mixed adoption of this treatment scheme, with some centers enrolling the majority of stage III/IVA patients, while others await further prospective data to clarify treatment strategies. The design of the GOG 258 significantly limits the general applicability of this trial which has been criticized for the discrepancy in the number of cycles of chemotherapy between treatment arms (4 cycles in the chemoradiation arm vs. 6 cycles in the chemotherapy only arm) and the sequence of therapy (EBRT followed by chemotherapy). Based on these significant limitations, it cannot be definitively concluded that adjuvant radiation offers no benefit in the treatment of advanced EC.

Although chemotherapy and radiation are frequently used in combination in the treatment of advanced EC, the optimal sequence of therapy continues to be debated. The sandwich method of therapy sequencing offers several theoretical benefits over alternative therapy sequences. First, the CRC sequence permits treatment of systemic disease up-front, while targeting potential micrometastatic disease in the pelvis and retroperitoneum in a timely fashion, and again controlling systemic disease after radiotherapy. Disadvantages to the administration of chemotherapy prior to radiation include increased toxicity and more radiation delays, which can lead to inferior oncologic outcomes. Additionally, complete irradiation of a tumor bed prior to the administration of chemotherapy leads to vascular alterations and can impair the delivery of chemotherapeutic agents, and therefore diminish the efficacy of subsequent systemic therapy [18,19]. In accordance with this, RC sequencing has been associated with delays in chemotherapy administration in patients with advanced endometrial cancer [20]. Therefore, the CRC regimen theoretically limits chemo-induced toxicity prior to EBRT, allowing for maximum therapeutic dosing of both chemotherapy and radiation [18-23]. Consistent with these observations, we observed a trend towards more retroperitoneal disease recurrence in the CR cohort compared to the CRC and RC sequences (19% vs. 8% and 6%, respectively). Additionally, we observed a trend towards greater treatment delay in the RC arm versus CRC and CR sequences (38% vs. 30% and 29%, respectively). The current study indicates that the sandwich sequence of chemoradiation is the most favorable sequence based on improved toxicity profile and superior survival outcomes.

Prior to the current report, other authors have investigated the CRC or “sandwich” approach to chemoradiation and observed positive outcomes. Fields et al. [20] and Lupe et al. [21] were of the first to prospectively evaluate the CRC sequence in advanced EC. Both reported similar outcomes in terms of 3-year PFS (54% and 53%, respectively) and 3-year OS (52% and 68%, respectively). Fields and colleague's study [20] was limited to only patients with serous histology. Similarly, Lupe and colleague's [21] cohort included was composed of >50% high-risk histology. Our results, 3-year PFS of 55% and OS of 71%, compared favorably to these reports which resemble our patient population.

Secord and colleagues [18] retrospectively evaluated patients with advanced EC treated with a combination of chemoradiation. They also observed a significant improvement in both PFS and OS when chemoradiation was delivered in CRC sequence compared to alternate sequencing [18]. The current study findings mirror those of Secord et al.'s and support the CRC therapy sequence. Our observed PFS and OS are lower than those reported by Secord et al. across all treatment cohorts, which is likely due to the difference in histologic subtypes between studies. In the current report, serous and clear cell histology represented 51% of the patient population, the percentage of histologies was well balanced between treatment cohorts. Comparatively, these histologies only represented 23% of patients in Secord et al.'s report. Serous and clear cell histology are known to carry a worse prognosis and higher recurrence rate at all stages compared to endometrioid adenocarcinoma [26,27]. Additionally, unlike Secord et al. [18], we did not include patients treated with whole-abdominal radiotherapy (WAR) as this approach is no longer considered an acceptable therapeutic option. In an effort to eliminate the heterogeneity of Secord et al.'s review [18], Lu and colleagues [24] reviewed their experience with sequential versus sandwich sequencing in a cohort of stage III endometrioid EC. These authors did not observe a significant difference in survival between adjuvant therapy sequences, however, the pelvic recurrence rate was markedly higher in the sequential cohort (30%) compared to the sandwich cohort (0%). This report is limited by its small sample size which only included 14 patients receiving adjuvant therapy in sandwich sequence.

The CRC sequence was evaluated prospectively in a phase II trial by Geller et al. examining the combination of carboplatin and docetaxel administered in sandwich with EBRT [22]. These authors reported a 3-year OS of 90% among patients receiving adjuvant therapy in CRC sequence which surpasses Secord et al. [18] as well as the current report. However, there were several key limitations of this study including lack of comparison cohort, small sample size, and use of docetaxel in lieu of the standard paclitaxel. At the time of this publication, the results of the GOG 209 which lead to carboplatin and paclitaxel taking over as the standard chemotherapy regimen for advanced EC had not yet been published [5]. The authors state that docetaxel was chosen to minimize neuropathy. Like Secord et al. [18], there were only a small number of patients with high-risk histology (only 12% serous histology and no clear cell histology) which likely skewed results towards improved PFS and OS as compared to the current study.

More recently, Goodman et al. [16] evaluated the sequence of adjuvant therapy in a cohort of locally advanced EC (stage III–IVA). They observed a significant improvement in OS among patients receiving CR compared to those receiving RC. However, they did not differentiate between patients receiving CRC or CR sequences. A recent prospective phase II evaluation of the CRC sequence in all stages of completely resected uterine serous carcinoma was conducted by Frimer et al. [23]. On analysis of patients with advanced disease, the median PFS was 22.3 months and the median OS was 28 months, comparing favorably to historical data. Again, the major limitations of the study include its lack of comparison arm and a large percentage of patients with early stage disease. Nevertheless, it supports the CRC sequence of therapy in high-risk histology and coincides with the results of the current study, in which 77% of all patients had high-risk histology. Based on the above evidence, our institution as well as many others have practiced chemoradiation delivered in sandwich sequence in an attempt to optimize patient outcomes.

The major limitation to the current study is its retrospective nature. Additionally, as this study spans an 18-year time period, there has been variation in the trends of specific chemotherapy regimens overtime. Despite this, the majority of patients received platinum-based chemotherapy and the use of specific chemotherapy regimens was balanced between treatment arms. Furthermore, we cannot account for factors that may have attributed to treatment sequence recommendations, including positive margins and residual disease status. Strengths of this study include a relatively large sample size in comparison to similar prior reports. Additionally, the present study included only completely surgical staged patients and was well balanced in terms of stage distribution and cytoreduction status. A noteworthy feature of the current study is its predominately African American patient population, due to the communities served by the participating institutions. Although the authors believe the key findings of the current report are transferable to other ethnicity groups and races, the race distribution of the current study likely accounts for the large proportion of high-risk histologic subtypes and high incidence of stage IIIC2 as well as IVB disease.

Despite the inherent limitations of a retrospective review, the current report demonstrates a significant improvement in both PFS and OS with chemoradiation delivered in sandwich sequence. The 14-month and 20-month improvement in OS over RC and CR sequencing, respectively, are clinically significant findings and warrant further prospective evaluation.

In conclusion, adjuvant therapy delivered in CRC sequence was associated with improvements in both PFS and OS in patients with advanced EC compared to alternant therapy sequencing.

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