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Clinical Investigation

A Multi-Institutional Analysis of Adjuvant Chemotherapy and Radiation Sequence in Women With Stage IIIC Endometrial Cancer

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Purpose: Our purpose was to evaluate the effect of sequence and type of adjuvant therapy for patients with stage IIIC endometrial carcinoma (EC) on outcomes.

Methods and Materials: In a multi-institutional retrospective cohort study, patients with stage IIIC EC who had surgical staging and received both adjuvant chemotherapy and radiation therapy (RT) were included. Adjuvant treatment regimens were classified as adjuvant chemotherapy followed by sequential RT (upfront chemo), which was predominant sequence; RT with concurrent chemotherapy followed by chemotherapy (concurrent); systemic chemotherapy before and after RT (sandwich); adjuvant RT followed by chemotherapy (upfront RT); or chemotherapy concurrent with vaginal cuff brachytherapy alone (chemo-brachy). Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by the Kaplan-Meier method.

Results: A total of 686 eligible patients were included with a median follow-up of 45.3 months. The estimated 5-year OS and RFS rates were 74% and 66%, respectively. The sequence and type of adjuvant therapy were not correlated with OS or RFS (adjusted $P = .68$ and .84, respectively). On multivariate analysis, black race, nonendometrioid histology, grade 3 tumor, stage IIIC2, and presence of adnexal and cervical involvement were associated with worse OS and RFS (all $P < .05$). Regardless of the sequence of treatment, the most common site of first recurrence was distant metastasis (20.1%). Vaginal only, pelvic only, and paraortic lymph node (PALN) recurrences occurred in 11 (1.6%),15 (2.2 %), and 43 (6.3 %) patients, respectively. Brachytherapy alone was associated with a higher rate of PALN recurrence (15%) compared with external beam radiation therapy (5%) $P < .0001$.

Conclusions: The sequence and type of combined adjuvant therapy did not affect OS or RFS rates. Brachytherapy alone was associated with a higher rate of PALN recurrence, emphasizing the role of nodal radiation for stage IIIC EC. The vast proportion of recurrences were distant despite systemic chemotherapy, highlighting the need for novel regimens.

Introduction

Endometrial cancer (EC) is the fourth most common cancer in women, with an estimated annual incidence of 65,620 new cases in the United States in 2020 and approximately 12,590 deaths.[1] Unlike many solid tumors, the incidence of EC has continued to increase the last several decades[1] and has been attributed to a decline in fertility rates, exogenous estrogen, diabetes, and obesity.[2,3] A recent population-based study that controlled for hysterectomy prevalence found that an increase in the age-adjusted incidence of nonendometrioid histologies across all races was responsible for this trend, and non-Hispanic black women had the lowest survival rates for all stages and histologies.[4]

Although locally advanced EC with lymph node metastasis only represents 8% to 10% of all EC cases,[5,6] recurrence rates are high despite adjuvant therapy, which translates into poor 5-year overall survival (OS) rates, ranging between 50% and 60%.[5] Adjuvant radiation therapy (RT) has been shown to reduce pelvic recurrence while chemotherapy reduces distant metastasis,[7] hence the rationale of combining both treatments to maximize locoregional and distant control. The recently published Post-Operative Radiation Therapy in Endometrial Cancer trial (PORTEC) 3 trial reported an OS benefit with the addition of chemotherapy during and after radiation compared with pelvic radiation therapy alone in high-risk stage I-III disease. Among patients with stage III disease, there was a 10% absolute improvement in failure-free survival and 12.5% improvement in OS with combined chemoradiation therapy compared with RT alone.[8] The Gynecologic Oncology Group (GOG) 258 trial evaluated the benefit of chemoradiation therapy over chemotherapy alone for stage III and IVA EC. The addition of RT to chemotherapy did not result in longer relapse-free survival at 5 years. The distant relapse rate was higher in patients who received upfront chemoradiation therapy compared with systemic chemotherapy alone, although vaginal and nodal recurrence rates were lower with the addition of adjuvant RT.[9]

Given the importance of both systemic and local therapies, national guidelines recommend multimodality approaches for stage IIIC EC[10,11]; however, the optimal sequencing of chemoradiation therapy remains controversial. As such, no prospective trial has compared different sequencing approaches. The purpose of this study was to evaluate clinical outcomes by the sequence and type of adjuvant chemoradiation therapy for patients with stage IIIC EC.

Methods and Materials

In a multi-institutional retrospective cohort study, clinical, surgical, and pathologic data from 13 academic centers were collected from September 1995 to July 2019 for patients with International Federation of Obstetrics and Gynecology (FIGO) 2009 stage IIIC EC after local institutional review board approval. Eligibility required surgical staging and receipt of adjuvant chemotherapy and RT. Patients with no recorded nodal sampling, those with carcinosarcoma histology, those who did not receive both adjuvant chemotherapy and RT, and those who received neoadjuvant chemotherapy were ineligible. The final patient cohort included 686 patients eligible for analysis. Patients with nodal and/or vaginal residual disease were included.

Surgical staging consisted of hysterectomy with salpingo-oophorectomy and lymph node assessment with or without pelvic washings. Treatment details including type of chemotherapy, number of concurrent and/or systemic chemotherapy cycles, radiation modality (external beam RT [EBRT], vaginal brachytherapy [BT]), radiation field extent, and delivered dose were recorded.

Adjuvant treatment regimens were classified by sequence type as adjuvant chemotherapy followed by sequential EBRT (upfront chemo), concurrent chemoradiation (EBRT) followed by chemotherapy (concurrent), systemic chemotherapy before and after EBRT (sandwich), adjuvant EBRT followed by chemotherapy (upfront RT), or chemotherapy delivered concurrent with vaginal cuff BT alone (chemo-brachy). The selection criteria for each sequencing approach was at the discretion of the physician and in line with each institution's practice.

Statistical analysis

Descriptive statistics were used to characterize baseline clinical and treatment characteristics with comparison by χ^2 or Fisher's exact test for the adjuvant sequence groups. OS was defined from surgery date to death of any cause. Recurrence-free survival (RFS) was defined from surgery date to date of first recurrence or progression or last follow-up. Time to endpoints were calculated by the Kaplan-Meier method. Recurrences were categorized into 4 categories: vaginal recurrence only, pelvic ± vaginal recurrences, paraortic lymph node (PALN) ± pelvic recurrences, and distant recurrences ± pelvic and PALN recurrences.

Univariable and multivariable analyses were performed by Cox proportional hazard models for RFS/OS. The variables that were significant ($P < .10$) on univariate analysis (UVA) were included in the multivariate analysis. Covariates evaluated by UVA were age, race, histology, tumor grade, FIGO 2009 stage, presence of 2 or more positive nodes, presence of adnexal and cervical involvement, lymphovascular invasion (LVSI), type and sequencing of adjuvant chemoradiation therapy, radiation field extent, and time from surgery to radiation as a continuous and dichotomous variable. Stepwise selection based on Akaike information criterion was used for model building. The Fine-Gray model was used to analyze the time to recurrence, and deaths without recurrence were considered competing risk events. Statistical analyses were conducted using Microsoft R Open 3.5.3 (https://mran.microsoft.com/) and SPSS version 27.

Results

Patient characteristics

A total of 686 eligible patients with stage IIIC EC were identified, and median follow-up was 45.3 months (interquartile range, [IQR] 23.4-71 months). Baseline characteristics of the patients are summarized in Table 1. Data were available and were collected for over 96% of total patients. The EBRT field size (pelvic vs extended field) was missing for 96 patients; the latter is explained by the fact that some patients were treated at community/regional centers and some data were unavailable for analysis.

Median age at diagnosis was 62 years (IQR, 55-70). Most patients had FIGO stage IIIC1 disease (64%), endometrioid histology (66%), and received a median number of 6 cycles of chemotherapy (71%). Pelvic nodal assessment was performed in 100% of patients, and pelvic and paraortic lymph node assessment was performed in 64.5% of patients (n = 443). A small percentage of patients (8%) had gross residual disease after surgery, mostly nodal (7%), and 1% had pelvic disease. Upfront chemo was the most common sequencing regimen (42.5%), followed by "sandwich" (25%) and concurrent regimens (16.5%). Most patients (58.5%) were treated with combination of EBRT and vaginal cuff BT, whereas 13.7% received BT alone. The proportion of PALN assessment was highest for patients treated with chemo-brachy (82%) and upfront RT (79%) and lowest for patients treated with the concurrent regimen (56%) ($P = .002$). BT was mostly but not exclusively delivered to patients with cervical involvement. Of the 249 patients with cervical involvement, 172 (69%) patients were treated with combination of EBRT and BT, and 225 patients (52%) without cervical involvement received a combination of EBRT and BT.

Age, race, depth of myometrial invasion, LVSI, number of positive lymph nodes, adnexal and cervical involvement, and stage were well balanced among all treatment sequencing arms (Table 1, all $P > .05$).

However, histology and grade were significantly different between the chemoradiation therapy sequencing arms. There were more endometrioid histologies in the concurrent arm (78% vs 61%-73% in the other sequencing arms), whereas there were more nonendometrioid histologies in the sandwich and chemo-brachy arms (36% and 39% vs 22% in concurrent, $P = .025$). There were significantly more grade 3 tumors in the sandwich treatment arm (60% vs 38%-54% in the other arms) ($P = .002$).

Treatment characteristics

The most commonly used chemotherapy regimen was carboplatin (area under the curve = 6) and paclitaxel (175 mg/m^2) every 3 weeks (89%). The median number of cycles delivered was 6 (IQR, 5-6). Other regimens included taxotere/adriamycin/cyclophosphamide, adriamycin/cisplatin, and platinum-based chemotherapy. Cisplatin was mainly used in combination with radiation. Most patients (79%) treated with concurrent chemoradiation received a total of 2 cycles of cisplatin while 15% of patients received cisplatin weekly followed by a median of 4 (IQR, 4-6)

Table 1 Distribution of risk factors among the chemoradiation therapy sequencing arms

58 (75%)	Entire cohort n = 686	Upfront chemo n = 292	Concurrent n = 113	Sandwich n = 170	Upfront RT n = 34	Chemo-brachy n = 77	*P* value
Age, median (IQR), y	62 (55-70)						
<60	280 (41%)	131 (45%)	42 (37%)	68 (40%)	15 (44%)	24 (31%)	.25
≥60	406 (59%)	161 (55%)	71 (63%)	102 (60%)	19 (56%)	53 (69%)	
Race							
Nonblack	568 (83%)	284 (89%)	96 (85%)	122 (72%)	29 (85%)	67 (87%)	.025
Black	90 (13%)	30 (11%)	17 (15%)	31 (18%)	4 (12%)	8 (11%)	
Histology							
Endometrioid	451 (66%)	187 (64%)	88 (78%)	104 (61%)	25 (73.5%)	47 (61%)	.025
Nonendometrioid	235 (34%)	105 (36%)	25 (22%)	66 (39%)	9 (26.5%)	30 (39%)	
Clear cell Ca	23 (3.4%)						
Serous Ca	130 (19.3%)						
Mixed Ca	70 (10.3%)						
Mucin Ca	5 (0.7%)						
Squamous cell Ca	1 (0.15)						
Grade							
1-2	328 (48%)	132 (46%)	69 (62%)	68 (40%)	19 (56%)	40 (52%)	.002
3	354 (52%)	157 (54%)	43 (38%)	102 (60%)	15 (44%)	37 (48%)	
Depth of myometrial invasion							
<50%	194 (28%)	84 (29%)	21 (19%)	55 (32%)	8 (23.5%)	26 (34%)	.07
≥50%	491 (72%)	208 (71%)	92 (81%)	115 (68%)	25 (73.5%)	51 (66%)	
LVSI							
Absent	145 (21%)	55 (19%)	28 (25.5%)	34 (20%)	9 (26.5%)	19 (25%)	.4
Present	529 (77%)	231 (81%)	82 (74.5%)	134 (80%)	24 (70.5%)	58 (75%)	
No. of positive lymph nodes							
<2	267 (39%)	118 (40%)	49 (43%)	52 (31%)	12 (35%)	36 (47%)	.07
≥2	419 (61%)	174 (56%)	64 (57%)	118 (69%)	22 (65%)	41 (53%)	
Adnexal involvement							
Absent	546 (81%)	222 (78%)	89 (80%)	147 (87.5%)	29 (85%)	59 (77%)	.1
Present	126 (19%)	62 (22%)	22 (20%)	21 (12.5%)	3 (9%)	18 (23%)	
Cervical involvement							
Absent	429 (62.5%)	191 (65%)	76 (67%)	103 (61%)	21 (62%)	48 (62%)	.7
Present	249 (36.5%)	101 (35%)	37 (33%)	67 (39%)	13 (38%)	28 (36%)	
FIGO stage							
IIIC1	439 (64%)	191 (65%)	76 (67%)	108 (63.5%)	22 (65%)	42 (54.5%)	.4
IIIC2	247 (36%)	101 (35%)	37 (34%)	62 (36.5%)	12 (35%)	35 (45.5%)	
Radiation treatment							
EBRT	191 (28%)	45 (15%)	43 (38%)	90 (53%)	13 (38%)	0	<.0001
BT	94 (14%)	14 (5%)	0	1 (0.6%)	2 (6%)	77 (100%)	
Both	401 (58%)	233 (79%)	70 (62%)	79 (46.4%)	19 (56%)	0	
Sequence of chemotherapy and RT							
Upfront chemo	292 (42.5%)						
Concurrent	113 (16.5%)						
Sandwich	170 (25%)						
Upfront RT	34 (5%)						
Chemo-brachy	77 (11%)						
Median no. of chemotherapy cycles (IQR)	6 (5-6)	6 (5-6)	4 (4-6)	6 (6-6)	6 (4-6)	6 (6-6)	NS

Abbreviations: BT = brachytherapy; Ca = carcinoma; EBRT = external beam radiation therapy; IQR = interquartile range 25th-75th percentile; LVSI = lymphovascular invasion; NS = not significant; RT = radiation therapy.

adjuvant chemotherapy cycles. No difference in compliance was seen between the different sequencing groups.

EBRT was delivered 5 days a week with a median dose of 45 Gy (range, 21.6-55 Gy) in 25 fractions (range, 12-32 fractions). Intracavitary vaginal high-dose-rate BT alone (without EBRT) was delivered to a median dose of 14 Gy in 2 fractions (12-30 Gy, 2-5 fractions) and to a median dose of 12 Gy in 3 fractions (5-32.5 Gy, 1-6 fractions) with EBRT.

Outcomes

A total of 168 deaths were reported for the entire cohort: 71 (24%) deaths in the upfront chemo group, 25 (22%) in the concurrent group, 36 (21%) in the sandwich group, 10 (29%) in the upfront RT group, and 26 (34%) in the chemo-brachy group ($P = .25$). Among the 168 deaths, 124 (74%) were related to EC, 31 (18%) were not related to disease, and 1 death was related to treatment. As for recurrences, a total of 201 (29%) occurred in the entire cohort: 84 (29%) recurrences in the upfront chemo group, 30 (26.5%) in the concurrent group, 51 (30%) in the sandwich group, 11 (32%) in the upfront RT group, and 25 (32.5%) in the chemo-brachy group ($P = .89$).

The estimated 5-year OS and RFS rates for the entire cohort were 74% and 66%, respectively. For endometrioid histology, the estimated 5-year RFS and OS were 74.4% and 83.6%, compared with 48.8% and 55.7% for non-endometrioid histology, respectively ($P < .0001$). By tumor grade, the estimated 5-year RFS and OS for patients with grade 1-2 tumors were 81.1% and 86.6%, compared with 50.0% and 59.2% for grade 3 disease, respectively ($P < .0001$).

On UVA for OS, older age, nonwhite race, non-endometrioid histology, grade 3 tumor, 2 or more positive nodes, deep myometrial invasion, adnexal involvement,

Table 2 Summary of univariate and multivariate analysis for survival endpoints

	UVA for OS		MVA for OS		UVA for RFS		MVA for RFS	
Variable	HR (unadjusted)	*P* value	HR	*P* value	HR	*P* value	HR	*P* value
Time from surgery to radiation: Increase by 1 wk	0.987	.030	NSFM	N/A	0.99	.22	NSFM	N/A
Age: ≥60 vs <60 y	1.625	.003	NSFM	N/A	1.328	.05	NSFM	N/A
Histology: Nonendometrioid vs endometrioid	2.743	<.0001	1.614	.012	2.2	<.0001	NSFM	N/A
Race: Black vs nonblack	2.557	<.0001	1.986	.001	1.8	.001	1.527	.023
Grade: 3 vs 1-2	3.417	<.0001	2.017	.001	3.06	<.0001	2.548	.000
Stage: IIIC2 vs IIIC1	1.614	.002	1.454	.021	1.51	.003	1.469	.010
Presence or absence of PALN dissection	1.2	.64	NSFM	N/A	1.05	.64	NSFM	N/A
No. of positive nodes: ≥2 vs <2	1.623	.004	NSFM	N/A	1.29	.076	NSFM	N/A
> 1 vs ≤ 1 positive PALN	2.04	<.0001	NSFM	N/A	1.65	.003	NSFM	N/A
Depth of myometrial invasion: ≥50% vs <50%	1.528	.024	1.344	.141	1.419	.034	NSFM	N/A
Adnexal involvement: Present vs absent	1.904	<.0001	1.706	.003	1.81	<.0001	1.550	.010
Cervical involvement: Present vs absent	1.816	<.0001	1.404	.046	1.69	<.0001	1.425	.021
LVSI: Present vs absent	1.402	.094	NSFM	N/A	1.36	.089	NSFM	N/A
Type of sequencing								
Concurrent vs upfront chemo	1.26	.3	NSFM	N/A	1.03	.88	NSFM	N/A
Sandwich vs upfront chemo	1.11	.59			1.1	.38		
Upfront RT vs upfront chemo	1.06	.83			1.07	.81		
Chemo-brachy vs upfront chemo	1.28	.27			1.12	.6		
Radiation type								
EBRT vs BT	1.02	.9	NSFM	N/A	.99	.9	NSFM	N/A
EBRT vs BT + EBRT	0.86	.4			1.1	.4		

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; HR = hazard ratio; LVSI = lymphovascular space invasion; MVA = multivariate analysis; N/A = not applicable; NSFM = not selected in final model; OS = overall survival; PALN = paraortic lymph node; RFS = recurrence-free survival; UVA = univariate analysis.

cervical involvement, and stage IIIC2 versus IIIC1 were associated with worse OS, as shown in Table 2.

A total of 44 deaths without recurrence were considered as competing risk events and were considered in the analysis of RFS. On UVA for RFS, older age, nonwhite race, nonendometrioid histology, grade 3 tumor, pelvic and PALN EBRT field versus pelvic field, deep myometrial invasion, LVSI, adnexal involvement, cervical involvement, and stage IIIC2 were associated with recurrence. More than 1 positive PALN ($P = .03$) was significantly associated with lower RFS rate and lower OS ($P < .0001$) rates.

The presence or absence of PALN assessmentwas not associated with OS or RFS.

The factors significantly associated with OS and RFS on multivariate analysis were race, histology, grade, stage, adnexal involvement, and cervical involvement (all $P < .05$). Specifically, black race, nonendometrioid histology, grade 3, stage IIIC2, and presence of adnexal and cervical involvement were associated with recurrence and worse survival (Table 2).

Sequencing and type of adjuvant therapy

The sequence and type of adjuvant therapy (upfront chemo vs concurrent vs sandwich vs upfront RT vs chemo-brachy) were not associated with hazard of OS or RFS (Table 2 and Figs. 1 and 2). As for the type of radiation delivered, (EBRT vs BT vs both), no association was found with hazard of OS and RFS. To overcome the imbalances between the different chemoradiation therapy arms, a stratified subgroup analysis was done for histology and for grade. The sequence and type of adjuvant therapy as well as the type of RT were not correlated with OS or RFS for endometrioid versus nonendometrioid histologies and for grade 1-2 versus 3.

A second subgroup analysis was performed excluding patients treated with chemo-brachy and upfront RT to strengthen the analysis and evaluate the 3 main sequencing approaches (upfront chemo, concurrent, and sandwich). There were no differences in OS and RFS among the 3 main sequencing approaches.

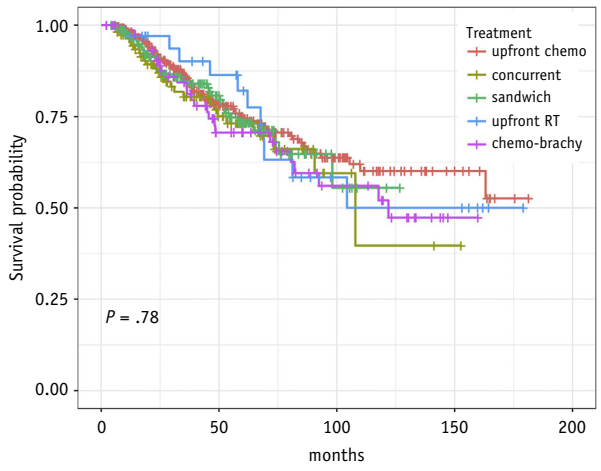

Fig. 1. Estimated overall survival (OS) Kaplan-Meier curves by sequencing type.

Factors associated with site of first recurrence

The most common site of first recurrence was distant metastasis (20.1%). Vaginal-only recurrence occurred in 11 patients (1.6%), and pelvic-only recurrence occurred in 15 patients (2.2%). Pelvic and vaginal recurrences occurred in 4 patients (0.6%) and PALN recurrences ± pelvic and vaginal recurrences occurred in 43 patients (6.3%). BT alone was associated with a higher rate of PALN ± pelvic recurrence (15%) compared with EBRT or the combination of EBRT and BT (5%) ($P < .0001$).

Discussion

This large multi-institutional study evaluated the importance of adjuvant chemotherapy and RT sequence in a cohort of 686 patients with stage IIIC EC. After a median follow-up of 45.3 months, no statistically significant difference was detected among 5 different sequencing regimens in terms of RFS and OS. Known prognostic factors, including black race, nonendometrioid histology, grade 3 tumor, stage IIIC2 disease, and presence of adnexal and cervical involvement, were associated with worse OS and RFS rates on multivariate analysis. Our results compare favorably with those of phase 3 randomized trials. Notably, the estimated 5-year RFS rate for this cohort was 74%, which compares favorably with the PORTEC 3 stage III subgroup (78.5%)[8] and the results of GOG-258 (59%).[9] In addition, similar to PORTEC 3, distant metastasis was the most common site of recurrence.

Combination chemoradiation therapy has been shown to yield superior long-term outcomes for locally advanced EC compared with a single modality approach.[8-11] Although the GOG-258 trial did not demonstrate a recurrence-free or survival benefit with the addition of RT to chemotherapy alone, patients who received chemotherapy alone had higher rates of vaginal (7% vs 2%) and pelvic and PALN recurrence (20% vs 11%),[9] which supports the role of adjuvant RT in preventing vaginal or nodal recurrence. In our study, the vaginal, pelvic, and PALN recurrence rates (without distant metastasis) were very low (1.6%, 2.2%, 6.3%) with chemoradiation therapy, highlighting the importance of adjuvant RT in pelvic control. Given the need to reduce the risk of distant metastasis while maximizing pelvic control in patients with stage IIIC EC, various sequencing regimens have been studied, with the rationale of using upfront chemotherapy to maximize distant control and upfront radiation to maximize pelvic control. The sandwich regimen is a compromise between the 2 approaches, although the regimen entails a break in systemic chemotherapy during the adjuvant RT course. There are no prospective trials that evaluate the importance

of adjuvant chemotherapy and RT sequence. Few studies have reported good clinical outcomes with "Sandwich" chemotherapy and RT while others reported on concurrent chemoradiation followed by additional chemotherapy[18,19] or RT upfront followed by chemotherapy.[20] The concurrent regimen was initially evaluated in a phase 2 Radiation Therapy Oncology Group study with excellent reported clinical results[18] and was adapted as the experimental arm in the GOG-258 and PORTEC-3 studies. A major criticism of the concurrent regimen is the delay in the delivery of systemic doses of chemotherapy, which may have been responsible for the higher rate of distant metastasis observed in the concurrent arm of the GOG-258 study.[18]

When comparing treatment sequence, small retrospective studies have shown no difference in outcomes between upfront chemotherapy followed by adjuvant RT and the sandwich regimen for stage III EC.[21,22] The sandwich regimen was found to be feasible and well tolerated, although it was associated with more hematologic toxicity and treatment breaks than upfront chemotherapy followed by RT.[15,23,24] A National Cancer Data Base study evaluated survival outcomes in women with node-positive EC receiving different sequencing of adjuvant therapy. A total of 1826 patients with a median follow-up of 49.2 months were analyzed. The 5-year OS rate was significantly higher for upfront chemotherapy followed by RT compared with concurrent chemoradiation (67% vs 62%, $P = .004$), although the findings are limited by the study's retrospective nature and absence of a cancer-specific survival endpoint.[26]

Another observational cohort study reported on the optimal management of stage III-IV type 1 (grade 1-2 endometrioid) EC. A total of 5795 women were identified, of whom 1260 (21.7%) received EBRT only, 2465 (42.5%) received chemotherapy only, 593 (9.7%) received upfront EBRT before chemotherapy, and 1506 (26.0%) received upfront chemotherapy followed by EBRT. Upfront chemotherapy followed by EBRT was associated with longer OS compared with single-modality EBRT or chemotherapy or upfront EBRT followed by chemotherapy.[25] Although upfront chemotherapy followed by EBRT was associated with improved OS for patients with advanced stage grade 1-2 endometrioid cancers, these observational studies have limitations: OS is the only outcome available in observational studies, and cancer-specific survival outcomes and details on locoregional and distant recurrences are not reported. In addition, treatment details including dose, fractionation, and number of chemotherapy cycles planned and delivered are not available. When a stratified survival analysis restricted to patients with grade 1-2 endometrioid tumors was performed in this cohort, adjuvant therapy sequence was not associated with recurrence or survival.

In the subset of patients treated with vaginal BT alone in conjunction with chemotherapy, these patients were largely from an era in which surgical staging yielded on average 20 to 30 nodes, and the fear of toxicity from 3-dimensional conformal pelvic ± PALN RT outweighed its presumed benefit. However, given the very large number of locoregional failures (PALN ± pelvic recurrences) in the absence of EBRT (15% vs 5%) in this series, and in conjunction with the significant advances in surgical technique including use of sentinel nodes for staging, along with routine adaptation of intensity modulated RT resulting in improved tolerance and toxicity, this practice has fallen out of favor, and regional nodal treatment with pelvic ± PALN has become standard.

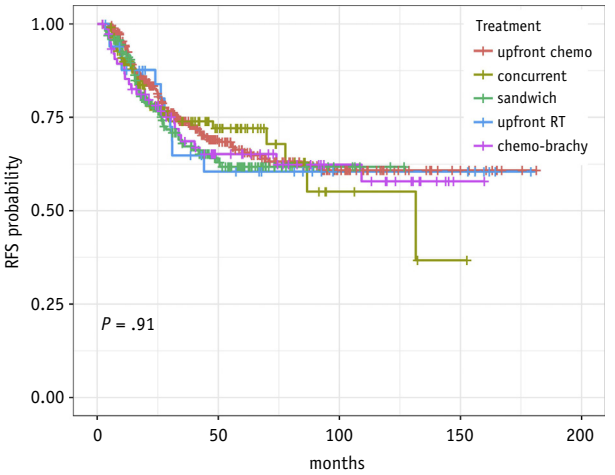

Fig. 2. Estimated recurrence-free survival (RFS) Kaplan-Meier curves by sequencing type.

Despite having the strength of a large multi-institutional cohort with robust follow-up, our study has several limitations. First, it is a retrospective study with inherent selection bias and heterogenous patient population. Additionally, toxicity data were not available from all participating institutions because the main goal was to evaluate the effect of chemoradiation therapy sequencing approaches on survival endpoints. Toxicity is very important, especially in the context of similar clinical outcomes, and will be addressed in a future research project.

Although all patients had stage IIIC EC, endometrioid and nonendometrioid histologies were included. Five different types of chemotherapy and RT sequencing approaches were included, which reflects the current practice across several institutions and adds to the controversy pertaining to the appropriate approach. The treatment arms were not balanced for all prognostic factors: The concurrent regimen had more patients with endometrioid histologies, whereas the sandwich and chemo-brachy regimens had more nonendometrioid histologies than the other arms. There were also significantly more grade 3 tumors in the sandwich treatment arm. The date of surgery was used as time zero to estimate the OS and RFS. The start date of chemotherapy and/or RT were not available for all patients because a large proportion of patients were referred to the academic center/main campus for part of their treatment. The authors acknowledge the controversial choice of selecting date of surgery as time zero in a retrospective

study. Finally, our study is unlikely to be powered to detect survival differences among the various sequencing regimens.

No randomized trial has yet evaluated the optimal sequencing approach for stage IIIC EC. Our study is the largest retrospective multi-institutional study reporting on the effect of adjuvant chemoradiotherapy sequencing on clinical outcomes for stage IIIC EC. This study represents the practice of 13 academic institutions across the United States between 1995 and 2019. Indeed, the locoregional recurrence rates of this study are similar to those of the GOG-258 concurrent chemoradiation therapy arm, and the distant recurrence rate is similar to the chemotherapy only arm,[9] again emphasizing the importance of both modalities. Despite use of adjuvant chemotherapy and radiation, distant recurrence remains the most common site of recurrence, and systemic regimens are needed given the clinical and biological heterogeneity of EC.

Conclusions

The sequence and type of combined adjuvant therapy did not affect OS or RFS rates, which were comparable to those of the prospective GOG 258 and PORTEC-3 studies. The prognostic risk factors for stage IIIC EC were race, histology, grade, stage, adnexal involvement, and cervical involvement. Adjuvant chemoradiation therapy resulted in excellent pelvic control. This was similar to that achieved by the randomized concurrent chemoradiation studies, confirming the efficacy of this regimen. BT alone was associated with a higher rate of PALN recurrence, emphasizing the role of nodal EBRT in stage IIIC EC. The vast proportion of recurrences were distant, despite systemic chemotherapy given early in the majority of patients, highlighting the need for novel systemic regimens to further improve outcomes.

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