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Original Article

Value of combined adjuvant chemotherapy and radiation on survival for stage III uterine cancer: is less radiation equal to more?

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Conflict of Interest
The authors declare that there are no conflicts of interest.

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ABSTRACT

Objective: Locally advanced endometrioid adenocarcinoma (LA-EAC) accounts for the majority of deaths for this cancer, yet there is no consensus on adjuvant treatment after surgery. Past studies suggest that combined modality treatment (CMT) may improve outcomes over treatment with chemotherapy (CT) or radiation therapy (RT, either external beam radiotherapy [EBRT] or vaginal brachytherapy [VBT]) alone. Using a large US-based population-based registry, we evaluated adjuvant CMT in LA-EAC and the relative benefit of regional EBRT compared to focused VBT.
Methods: We studied patients diagnosed with Stage III LA-EAC between 2004 and 2013 from the National Cancer Data Base (NCDB). We used Cox regression and a log-rank test to assess survival based on treatment with CT alone, EBRT alone, VBT alone, or CMT with EBRT and/or VBT. We used a χ^2 test to compare covariates between patients receiving CMT with EBRT or VBT.
Results: Patients who received CMT had better survival than those who received CT or EBRT/VBT alone. Compared to CMT with VBT, patients who received CMT with EBRT were slightly older and had more advanced-stage or positive nodes, and fewer had lymph node surgery. We found no survival difference between CMT with EBRT and CMT with VBT even when categorizing patients as high or low risk according to age, grade, and stage (low-risk p=0.3460; high-risk p=0.2158).
Conclusion: CMT was associated with superior survival outcomes compared to monotherapy. We observed no survival difference between radiation modalities in CMT, which highlights the effectiveness of a more focused treatment like brachytherapy.

Keywords: Carcinoma, Endometrioid; Stage III; Chemoradiotherapy; External Beam Radiation; Brachytherapy

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INTRODUCTION

Cancer of the uterine corpus is the 6th most common malignancy in women worldwide and the 4th most common malignancy for women in developed countries [1,2]. The predominant histology is endometrioid adenocarcinoma, which constitutes approximately 80% of cases [3]. While survival rates for early-stage disease exceed 90%, survival rates are much lower (approximately 60%) for patients with locally advanced endometrioid adenocarcinoma (LA-EAC) (stage IIIA–IIIC disease), which, though less common, accounts for most deaths from this cancer [4].

Standard of care treatment for LA-EAC includes total hysterectomy with bilateral salpingo-oophorectomy and surgical lymph node (LN) staging [5]. An optimal adjuvant therapy for LA-EAC has not been established. The Gynecologic Oncology Group (GOG) 122 study demonstrated improved survival with adjuvant chemotherapy (CT) compared to radiation therapy (RT) alone in advanced endometrial cancer (EC), though disease recurrences were high in both arms [6]. GOG 184, which compared 2 CT regimens after adjuvant RT [7], and Radiation Therapy Oncology Group (RTOG) 9708, which tested RT with concurrent cisplatin-based CT [8], demonstrated superior outcomes with adjuvant combined modality treatment (CMT) compared to monotherapy using historic controls. This study will evaluate the use and impact of CMT and compare the contributions of regional radiation and focused vaginal brachytherapy (VBT) in the adjuvant setting for patients with stage III endometrioid adenocarcinoma.

MATERIALS AND METHODS

1. Patients and data extraction

We obtained patient and outcomes data from the National Cancer Data Base (NCDB), a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons that has collected nationwide, facility-based comprehensive clinical data from accredited hospitals since 1989. The current NCDB captures approximately 70% of all newly diagnosed malignancies in the US annually with de-identified patient information.

This study included patients with stage III endometrioid EC (International Federation of Gynecology and Obstetrics [FIGO] 2009 which excluded positive cytology) diagnosed from 2004 to 2013 who received adjuvant therapy in the NCDB. Patients who did not receive adjuvant therapy or who had non-endometrioid adenocarcinoma histology (e.g., papillary serous carcinoma, lymphoma, sarcoma, small cell carcinoma, etc.) were excluded. Patients with early-stage (stage I–II), with positive cytology, with metastatic disease, or who received radiation to sites other than the pelvis were also excluded. Patients were grouped according to the adjuvant therapy they received. Patients who received CT and external beam radiotherapy (EBRT) with or without VBT were grouped into CT with EBRT. Patients who did not receive CT were excluded. We included all stage III sub-stages (ABC), as they are treated similarly in practice and bundled together on clinical trials.

Patient demographic information, including patient age, race, insurance status, Charlson-Deyo comorbidity score, and geographic region, were analyzed as covariates. Clinical information, including staging, tumor size, LN surgery, grade, lymphovascular invasion (LVI), and nodal status, were also included as covariates. Patients with known risk factors, including age ≥60, grade 3 or 4 disease, or stage IIIC status, were grouped as high-risk, while

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patients with none of these factors were grouped as low-risk. Surgical margin status was not included due to the limited available data.

2. Statistical analysis

We assessed differences in sociodemographic and tumor characteristics by radiation treatment cohorts using the χ^2 test for all variables. We assessed the temporal trend of different CMT modalities (EBRT and/or VBT) by analysis of variance (ANOVA), using the year of diagnosis as a covariate. We calculated age-adjusted incidence with 19 age groups and standardized to the 2000 US Standard Population, with 95% confidence intervals (CIs) calculated using the Tiwari's modification [17]. We used univariate Cox proportional hazard models to test for covariates with significant differences in survival, followed by a multivariate Cox model containing all variables that met the $p<0.05$ criteria. We report multivariate analysis results using hazard ratios (HRs) with 95% CIs to show which covariates independently predict survival. We used Kaplan-Meier curves and log-rank analyses to demonstrate differences in survival by adjuvant treatment modality. We completed all analyses at the 0.05 2-sided significance level in SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

1. Patients

We identified a total of 8,738 patients from the NCDB with stage III endometrioid adenocarcinoma who received adjuvant therapy (**Fig. 1**). Of these, 4,861 patients received CT

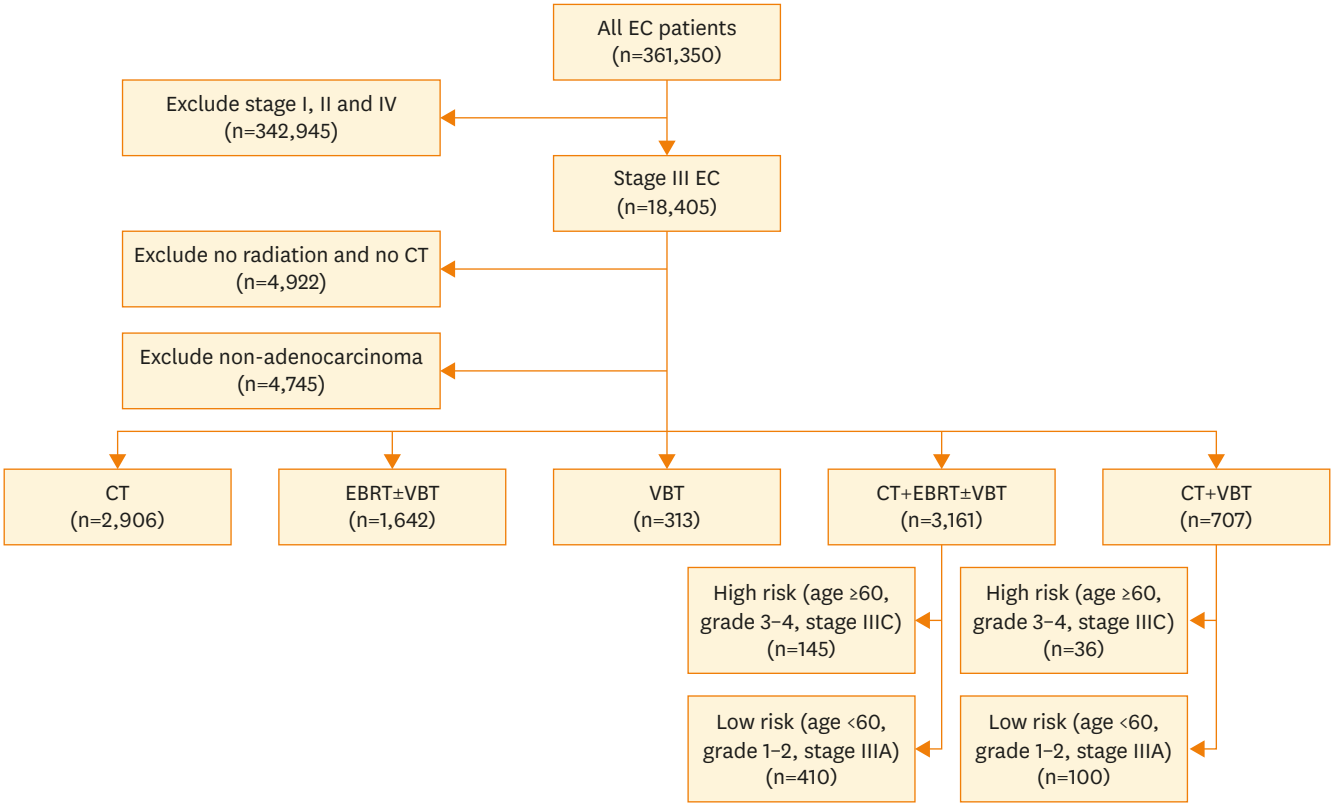

Fig. 1. CONSORT diagram of patients with stage III endometrioid adenocarcinoma from NCDB receiving adjuvant therapy.
CT, chemotherapy; EBRT, external beam radiotherapy; EC, endometrial cancer; NCDB, National Cancer Data Base; RT, radiation therapy; VBT, vaginal brachytherapy.

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or RT, but not both (monotherapy). A total of 3,868 patients received CMT with both CT and RT. Most of those patients (81.7%) were treated with CT and EBRT (with or without VBT), while a minority (18.3%) received CT with VBT as the sole RT modality.

2. Adjuvant radiation use and its temporal patterns

We analyzed the temporal pattern of adjuvant radiation use and found that the overall use of RT decreased over time, but the use of CMT increased significantly during the study period (**Supplementary Fig. 1**). The percentage of stage III patients who received CT with EBRT increased from 22.8% to 33.2% from 2004 to 2013 (0.96% per year; 95% CI=0.44–1.47; p=0.003). Though the absolute number of stage III patients who received CT with VBT decreased, the percentage also increased from 2.3% in 2004 to 6.1% in 2013 (0.54% per year, 95%CI 0.30–0.78, p=0.001).

3. RT in CMT

We analyzed factors associated with the choice of adjuvant RT modality in the CMT group and compared patient demographics and pathologic information between patients receiving combined therapy with EBRT or VBT (**Table 1**). Patients receiving CT and VBT were younger and lower-stage, and more had negative nodal status. The median ages for patients receiving CT with EBRT and CT with VBT were 59 (interquartile range [IQR]=53–67) and 61 (IQR=54–68), respectively. Practice patterns varied among different geographic regions (p<0.001). The Northeast region had the highest percentage of patients receiving VBT only with CT (105/271, 38.7%), while the Pacific region had the lowest percentage (38/486, 7.8%). A slightly higher percentage of patients who were neither white nor black received CT with EBRT than patients who were white or black (88.9% vs. 80.0%–81.6%; p=0.032). A higher percentage of patients who received CT with EBRT underwent LN surgery than patients who received CT with VBT (19.2% vs. 15.3%; p=0.017).

4. Survival outcomes and adjuvant therapy (emphasis on regional [EBRT] compared to focal [VBT] radiation)

We evaluated overall survival (OS) according to adjuvant therapy received (**Fig. 2** and **Supplementary Table 1**). In the monotherapy group, CT alone was associated with improved survival compared to EBRT alone at 5 years (58.7% vs. 52.7%; 95% CI=56.3%–61.0% vs 49.9%–55.4%; p<0.001). Patients receiving CMT exhibited significantly improved OS compared to patients receiving monotherapy with either RT or CT alone (p<0.001). For patients receiving CMT, age ≥60, race, stage, LN surgery, and histologic grade remained significant predictors for mortality upon multivariate analysis in either radiation modality (**Table 2**). When comparing the adjuvant RT modalities in the CMT groups, we found no significant difference in the 5-year OS rates between CT with EBRT (regional) and CT with VBT (focused RT): 66.3% (95% CI=64.1%–68.4%) and 70.7% (95% CI=66.1%–74.8%), respectively, (p=0.376).

To further study the impact of regional or focal radiation, we stratified the CMT patients as high-risk or low-risk, according to the known clinical prognostic factors (age ≥60, grade 3 or 4 disease, or stage IIIC status). This was a smaller subgroup analysis (<20% of the entire group), as not all patients had complete information, yet the groups were proportionally equivalent for the EBRT (17.6%) and VBT (19.2%) arms (p=0.292). The low-risk stage III patients had significantly better 5-year OS than the high-risk group (89.9% vs. 43.6%, respectively; p<0.001), as expected. The number of high and low risk patients in the CT with EBRT and CT with VBT groups did not differ significantly; approximately 26% of patients in both groups were high-risk (p=0.935).

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Table 1. Demographics and clinical characteristics according to adjuvant CMT

Characteristics	CT+EBRT (n=3,161)	CT+VBT (n=707)	p
Age (yr)			0.006
<60	1,560 (49.4)	389 (55.0)	
≥60	1,601 (50.6)	318 (45.0)	
Race			0.032
White	2,703 (86.6)	609 (87.8)	
Black	260 (8.3)	65 (9.4)	
Other	160 (5.1)	20 (2.9)	
Median miles from hospital (IQR)	10.7 (4.7–25.2)	12.3 (5.6–26.1)	0.008
Charlson-Deyo score			0.547
0	2,460 (77.8)	539 (76.2)	
1	579 (18.3)	142 (20.1)	
2	122 (3.9)	26 (3.7)	
Geographic location			<0.001
Central	1,182 (38.6)	284 (41.6)	
Mountains	142 (4.6)	26 (3.8)	
Northeast	166 (5.4)	105 (15.4)	
Pacific	448 (14.6)	38 (5.6)	
Southeast	1,125 (36.7)	230 (33.7)	
LN surgery			0.017
No LN surgery	603 (19.2)	108 (15.3)	
LN surgery	2,534 (80.8)	596 (84.7)	
Pathological stage			<0.001
3A	1,215 (43.7)	354 (53.9)	
3B	295 (10.6)	66 (10.0)	
3C	1,193 (42.9)	212 (32.3)	
3NOS	76 (2.7)	25 (3.8)	
Grade			0.810
1 or 2	1,472 (46.6)	320 (45.3)	
3 or 4	1,259 (39.8)	287 (40.6)	
Unknown	430 (13.6)	100 (14.1)	
FIGO grade (2010–2013)			0.711
Type I	428 (23.4)	105 (23.9)	
Type II	303 (16.6)	79 (18.0)	
Unknown	1,097 (60.0)	255 (58.1)	
Pelvic node status (2010–2013)			<0.001
Negative	817 (44.7)	250 (56.9)	
Positive	596 (32.6)	111 (25.3)	
Unknown	415 (22.7)	78 (17.8)	
Para-aortic node status (2010–2013)			<0.001
Negative	696 (38.1)	221 (50.3)	
Positive	266 (14.6)	55 (12.5)	
Unknown	866 (47.4)	163 (37.1)	

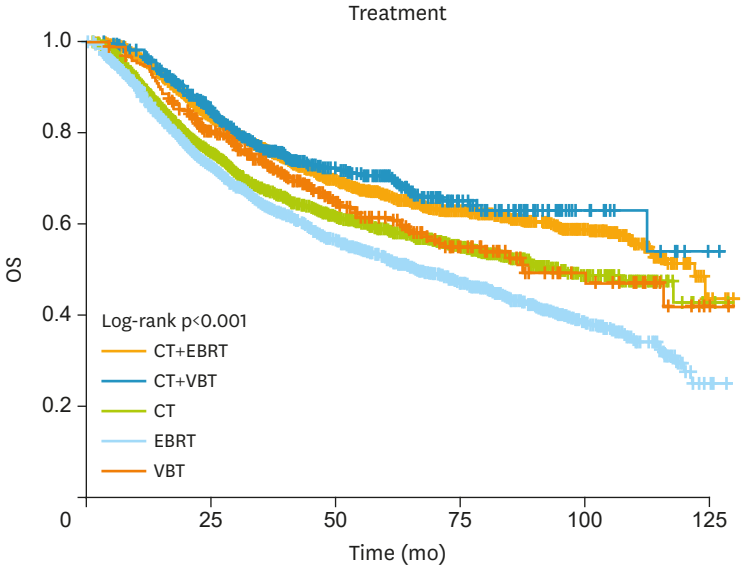
Values are presented as number of patients (%) not otherwise specified.
CMT, combined modality treatment; CT, chemotherapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LN, lymph node; VBT, vaginal brachytherapy.

We evaluated OS differences between CT with EBRT and CT with VBT according to high- or low-risk group for the patients with available clinical information (**Fig. 3**). We found no significant difference in OS based on adjuvant RT modality for low risk patients who received CMT (5-year survival for CT with EBRT and CT with VBT, 90.5% vs. 87.1%, respectively; p=0.346). There was also no statistically significant difference in survival between CT with EBRT and CT with VBT for the high-risk patients (5-year survival for CT with EBRT and CT with VBT, 45.5% vs. 36.6%, respectively; p=0.216), though the small sample size and under-powered subgroup analysis prevent us from excluding the possibility of such trends conclusively.

Table 2. Multivariate analysis of survival by CMT

Characteristics	CT+EBRT		CT+VBT	
	HR (95% CI)	p	HR (95% CI)	p
Age (yr)				
<60	Reference		Reference	
≥60	1.94 (1.64–2.30)	<0.001	2.52 (1.67–3.80)	<0.001
Race				
White	Reference		Reference	
Black	1.49 (1.17–1.91)	0.001	1.27 (0.75–2.15)	0.375
Other	1.13 (0.76–1.67)	0.557	2.91 (1.02–8.25)	0.045
Charlson-Deyo score				
0	Reference		Reference	
1	1.39 (1.14–1.69)	0.001	1.00 (0.66–1.54)	0.983
2	1.41 (0.99–2.01)	0.058	4.96 (2.57–9.57)	<0.001
LN surgery				
No LN surgery	Reference		-	
LN surgery	0.42 (0.33–0.53)	<0.001	-	
Pathological stage				
3A	Reference		Reference	
3B	1.47 (1.10–1.96)	0.009	2.27 (1.24–4.16)	0.008
3C	2.16 (1.78–2.62)	<0.001	2.81 (1.90–4.15)	<0.001
3NOS	1.22 (0.73–2.04)	0.445	0.42 (0.10–1.77)	0.237
Grade				
1 or 2	Reference		Reference	
3 or 4	1.88 (1.57–2.24)	<0.001	1.44 (0.98–2.12)	0.065
Unknown	1.41 (1.05–1.89)	0.022	1.24 (0.69–2.23)	0.474

CI, confidence interval; CMT, combined modality treatment; CT, chemotherapy; EBRT, external beam radiotherapy; HR, hazard ratio; LN, lymph node; VBT, vaginal brachytherapy; NOS, non-organ specific.



	No.	5-year OS (95% CI)	HR (95% CI)	p
Therapy combination				
CT	2,417	58.7 (56.3–61.0)	Reference	
EBRT	1,509	52.7 (49.9–55.4)	1.22 (1.11–1.35)	<0.001
VBT	286	61.2 (54.7–67.2)	0.88 (0.73–1.08)	0.218
CT+EBRT	2,615	66.3 (64.1–68.4)	0.71 (0.64–0.78)	<0.001
CT+VBT	608	70.7 (66.1–74.8)	0.65 (0.55–0.78)	<0.001

Fig. 2. Survival of patients with LA-EAC according to adjuvant treatment modality. CMT with either EBRT or VBT had better survival compared to monotherapy. CI, confidence interval; CMT, combined modality treatment; CT, chemotherapy; EBRT, external beam radiotherapy; HR, hazard ratio; LA-EAC, locally advanced endometrioid adenocarcinoma; OS, overall survival; VBT, vaginal brachytherapy.

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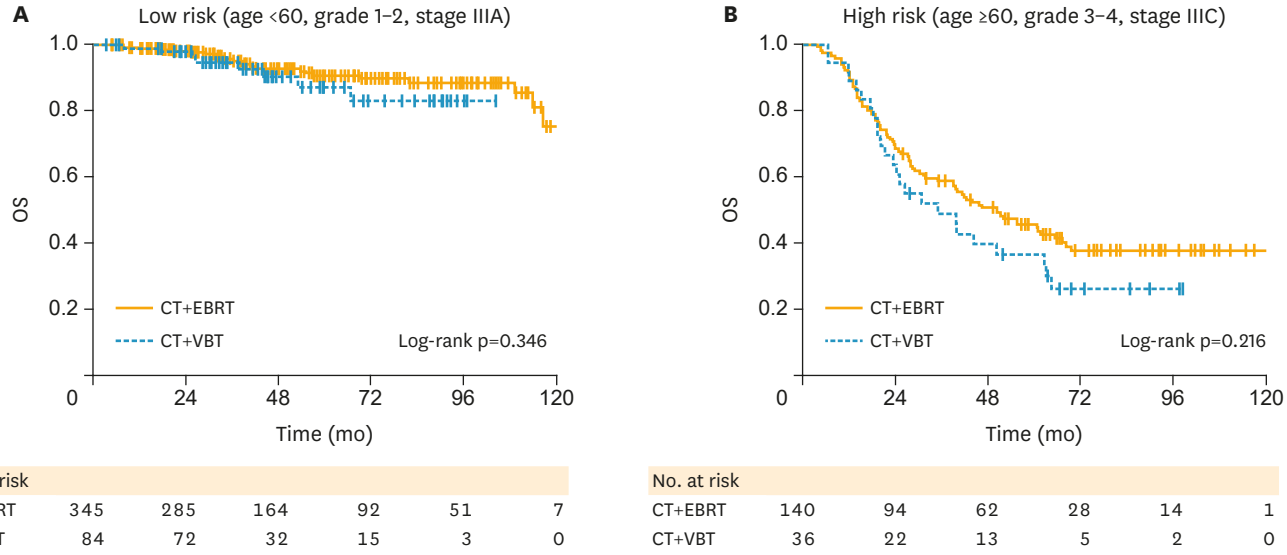

No. at risk						
CT+EBRT	345	285	164	92	51	7
CT+VBT	84	72	32	15	3	0

No. at risk						
CT+EBRT	140	94	62	28	14	1
CT+VBT	36	22	13	5	2	0

Fig. 3. Survival of patients receiving adjuvant hemoradiation. (A) Low-risk (age <60, grade 1–2, stage IIIA) patients according to type of adjuvant radiation modality. (B) High-risk (age >60, grade 3–4, stage IIIC) patients according to type of adjuvant radiation modality.
CT, chemotherapy; EBRT, external beam radiotherapy; OS, overall survival; VBT, vaginal brachytherapy.

DISCUSSION

Despite treatment advances and improved staging accuracy, the death rate for cancer of the uterine corpus in the US has exhibited a statistically significant 1.4% increase of the adjusted annual percentage change from 2005–2014 [9]. Although the GOG 122 study contributed to the shift towards using adjuvant CT in many practices, the disease recurrence in both the CT and RT arms exceeded 50%, with significant loco-regional failure [6]. Two additional prospective studies comparing EC patients (including high-risk patients) treated with adjuvant CT or RT failed to show CT's superiority over RT in terms of OS but suggested that RT may impact local progression while CT may enhance distant disease control [10,11]. Together, these studies highlight the importance of selecting advanced EC patients that may benefit from combined modality therapy and tailoring treatment accordingly. After GOG 122 showed a survival benefit for adjuvant CT over whole-abdominal irradiation, radiation use has decreased, which may be negatively affecting cancer survival [12].

Several prospective studies investigating different CMT strategies for locally advanced EC have suggested potential oncologic benefits, but the results have not been definitive [7,8,13]. A combined analysis from two European randomized trials using adjuvant pelvic radiation followed by sequential CT or observation showed reduced disease progression and improved OS in patients treated with combined modality therapy [13]. Similarly, the GOG 184 study showed a low loco-regional recurrence rate of 10% at 3 years using sequential adjuvant pelvic radiation followed by CT [7], which was numerically superior to the outcomes of GOG 122. RTOG 9708 tested a different approach using concurrent chemoradiation, which also included a VBT boost and additional adjuvant CT. The results showed the feasibility of concurrent chemoradiation therapy and the potential for reduced local failure and improved survival compared to GOG 122 [8].

Recently, several studies using the NCDB have investigated the effects of postoperative RT on stage III EC. Boothe et al. [14] reported that stage III patients who received CMT had

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better survival outcomes than patients treated with monotherapy (either RT or CT alone), which is consistent with our findings. Rauh-Hain et al. [15] reported that patients aged > 75 years with high-grade, advanced-stage EC are less likely to receive adjuvant therapy, but forgoing adjuvant therapy – whether CT, RT, or both – was associated with an increased risk of all-cause mortality after correcting for other prognostic factors. In addition, smaller institutional series, where radiation treatment plans are available, have demonstrated that combined modality therapy may reduce loco-regional recurrence, which may translate to a survival benefit [16-22]. However, none of these studies looks separately at focused RT (brachytherapy) alone. Recently presented preliminary results from GOG 258, which investigates the use of adjuvant CT alone (carboplatin/paclitaxel) versus concurrent chemoradiation in high-risk EC after optimal debulking surgery, showed that CMT reduced the rate of local recurrence compared to CT but did not increase recurrence-free survival [23]. The European PORTEC-3 trial showed that adding concurrent cisplatin CT to pelvic radiation improved 5 year failure-free survival in stage III EC patients by 11% over pelvic radiation alone [24]. Our study is consistent with these retrospective and prospective studies, which demonstrated that CMT should be considered for locally advanced EC and that selecting patients for optimal therapies may be critical to achieving desired clinical endpoints. However, our results were unique, because we also compared the effects of EBRT (regional) to VBT (focal) in the CMT setting and found no benefit for one over the other, but still showed the benefit of CMT over monotherapy.

Vaginal cuff brachytherapy (VBT) is a well-established local therapy for early-stage EC after surgical resection, and VBT can be added after pelvic irradiation for patients with early-stage disease to provide excellent loco-regional control [25]. However, VBT's effects on high risk or locally advanced EC are less defined. A retrospective analysis from University of California Davis showed a non-significant trend towards improved pelvic control when VBT was added to EBRT [26]. Another recent NCDB study showed that adding VBT to EBRT was associated with improved survival in Stage III patients with cervical involvement [27]. Although our study can definitively show neither superiority nor non-inferiority between CMT with VBT alone and CMT modalities incorporating EBRT, there is a growing trend to use brachytherapy alone as the adjuvant radiation modality for both early [28] and advanced endometrioid cancer [12]. In the current NDCB dataset, we demonstrated that the rate of CMT with VBT alone in patients with locally advanced EC increased over the study period. In a recent institutional series from Yale, adjuvant carboplatin and paclitaxel followed by VBT for stage III EC achieved excellent overall and disease free survival in lower grade, node-negative patients. There were no cases of isolated vaginal recurrence in this series, suggesting the benefit of focal vaginal therapy in selected surgically-staged locally advanced patients [29]. Our results indicated that using VBT with CT was also associated with improved survival over monotherapy even after correcting for other factors in a multivariate analysis, and there was no statistical survival difference between EBRT with or without VBT with CT and VBT alone with CT in low-risk stage III patients. In the high-risk patients, we cannot exclude the possibility that our sample size was insufficient to significantly discriminate small differences in selected subgroups, as the survival curves did tend to separate. However, our data may reflect a selection bias against patients who received VBT alone, as they may not have been considered candidates for EBRT because of their comorbidities. Whether VBT was a surrogate for other neglected clinical factors, such as localized disease or lower disease burden, or has direct clinical benefit when combined with CT, remains inconclusive and should be explored further.

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Our study is limited by the inherit nature of a population-based retrospective database, which lacks data on treatment compliance or quality assurance, pattern of failure, salvage therapy, and treatment complications. It is also limited by incomplete data entry for known prognostic factors, such as LVI and/or residual disease, as well as other unknown confounding factors. The NCDB also lacks data on recurrence and treatment toxicity, which limits its usefulness. Therefore, it cannot provide definitive evidence for treatment recommendation. However, a large population-based study such as this can still provide insights on practice patterns and treatment variance among different geographic regions, which can be generalized to daily clinical practice. Our analysis from the NCDB showed substantial regional variation in practice with regard to adjuvant radiotherapy. Specifically, more patients in the Pacific region received adjuvant EBRT with CT (approximately 92% of patients received chemoradiation), while in other regions, higher percentages received adjuvant VBT with CT (15-38%). The Pacific region showed the highest survival compared to other regions (66.4%, HR=0.80; range=0.07–0.92; p=0.0014) on univariate analysis, suggesting the opportunity to improve adjuvant therapy if it can be standardized across regions.

In conclusion, patients with stage III endometrioid adenocarcinoma appear to benefit from CMT with CT and RT, whether EBRT, VBT, or both. Prospective studies with proper patient selection for this heterogeneous population are needed to definitively provide appropriate adjuvant treatment recommendations to further improve and optimize outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Multivariate analysis for OS in patients receiving CMT

Click here to view

Supplementary Fig. 1

Temporal trend of radiation use. (A) Radiation utilization over time regardless of CT use; (B) radiation utilization over time in the CMT group.

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