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Adjuvant vaginal brachytherapy and chemotherapy versus pelvic radiotherapy in early-stage endometrial cancer: Outcomes by risk factors

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HIGHLIGHTS

- The NCDB was reviewed to compare treatments for various subgroups of patients with endometrial cancer.
- The addition of chemotherapy results in an improved survival for serous histology but not for other subgroups.
- Certain constellations of risk factors appear to benefit from external beam radiotherapy.

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ABSTRACT

Objective: To report on patterns of care as well as evaluate the two treatment regimens using a large retrospective hospital-based registry to identify possible subgroups of patients who may experience benefit with VBT + CT vs. EBRT.

Methods: Patients from the National Cancer Database (NCDB) were identified who met the inclusion criteria for GOG 249 and were treated with either VBT + CT or WPRT. Demographic, clinicopathologic, and treatment factors were collected. Association of treatment type and other variables with overall survival was analyzed using Cox proportional hazards model. Subset analyses were performed based on a variety of risk factors, including high risk pathologies, surgical nodal sampling, and grade.

Results: A total of 4,602 patients were included in the analysis, with 41% receiving VBT + CT and 59% receiving WPRT. For the entire cohort, VBT + CT was associated with improved survival, with 3-year overall survival 89.6% vs. 87.8% (hazard ratio 1.24, 95%CI 1.01–1.52, p = 0.04). On subset analysis, patients with serous histology experienced benefit with VBT + CT, while high-grade endometrial patients without lymph node dissection experienced improved survival associated with EBRT. After exclusion of serous histology, there was no survival difference associated with treatment type.

Conclusions: VBT + CT was associated with superior survival outcomes in patients with early-stage serous carcinoma. For non-serous histology, treatment modality was not associated with a difference in survival, although patients with high-grade disease and no nodal dissection experienced benefit from EBRT.

1. Introduction

Standard of care management of early-stage endometrial cancer includes simple hysterectomy, with adjuvant therapy recommended for those with high risk clinical and pathologic features. These risk factors include depth of myometrial invasion, lymphovascular space invasion (LVSI) [1–3], high pathologic grade [1,3], aggressive histologies (i.e. serous) [4], and older age [1,5,6]. Early stage (FIGO I-II) patients with varying combinations of high-risk features are collectively considered to be at a "high-intermediate risk (HIR)" for recurrence. Adjuvant therapies can include whole pelvic radiation therapy (WPRT), brachytherapy directed to the vaginal cuff alone (VBT), and/or chemotherapy (typically carboplatin and paclitaxel).

The use of adjuvant radiation therapy was assessed in GOG 99 [7], in which investigators identified a HIR subset that experienced a locoregional control benefit with adjuvant whole pelvic radiation therapy. PORTEC-1 also revealed a benefit for a similarly defined HIR population [8]. Based on patterns of failure data demonstrating that most recurrences occurred at the vaginal cuff, brachytherapy directed to this region was also studied and found to be efficacious

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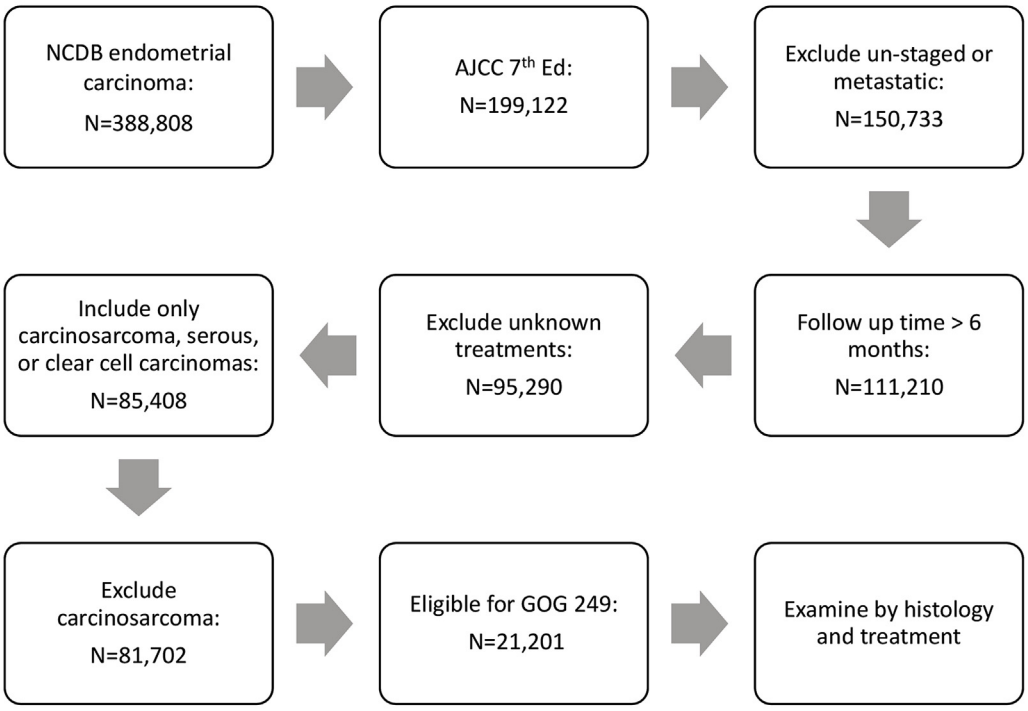
A



Histologic Subtype	Treatment					
	None	VBT	VBT+CT	EBRT	EBRT+CT	Chemo
Endometrioid	8,157	4,435	885	2,531	505	566
Serous	1,070	174	880	122	286	830
Clear Cell	312	61	132	52	63	140

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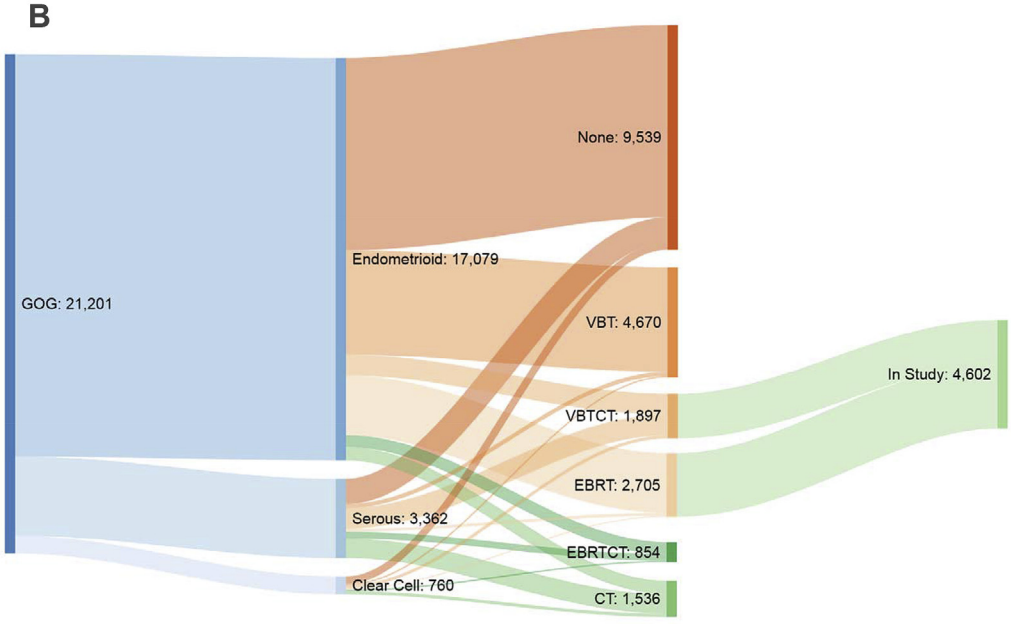

Fig. 1. A) Flow chart demonstrating patient selection. B) Sankey diagram of treatment by histologic subtype. NCDB = National Cancer Database. VBT = vaginal brachytherapy. CT = chemotherapy.

Table 1
Patient characteristics by treatment group. CMI describes the Charlson Comorbidity Index. Stage I are those patients coded as stage I but without data on whether they are stage IA or IB. Education is an estimate of the percentage of people in an individual's zip code who did not graduate from high school. Significance was evaluated using chi-squared testing.

Characteristic	All	(%)	VBT + CT	(%)	EBRT	(%)	P-value
N	4602	100	1897	41.2	2705	58.8	
Age (years)							
<50	216	4.7	60	3.2	156	5.8	<0.001
50-70	1617	35.1	625	32.9	992	36.7	
≥70	2769	60.2	1212	63.9	1557	57.6	
Charlson Comorbidity Index	0	0.0					0.078
0	3423	74.4	1430	75.4	1993	73.7	
1	967	21.0	395	20.8	572	21.1	
2	212	4.6	72	3.8	140	5.2	
Median Income							<0.001
<$38,000	753	16.4	272	14.3	481	17.8	
$38,000-$47,999	1060	23.0	373	19.7	687	25.4	
$48,000-$62,999	1215	26.4	500	26.4	715	26.4	
>$63,000	1564	34.0	749	39.5	815	30.1	
Grade							<0.001
Well-differentiated	571	12.4	93	4.9	478	17.7	
Moderately-differentiated	1366	29.7	294	15.5	1072	39.6	
Poorly-differentiated	1687	36.7	951	50.1	736	27.2	
Undifferentiated	285	6.2	199	10.5	86	3.2	
Unknown	693	15.1	360	19.0	333	12.3	
Histology							<0.001
Endometrioid	3416	74.2	885	46.7	2531	93.6	
Serous	1002	21.8	880	46.4	122	4.5	
Clear Cell	184	4.0	132	7.0	52	1.9	
FIGO Stage							<0.001
I	19	0.4	11	0.6	8	0.3	
IA	1141	24.8	864	45.5	277	10.2	
IB	1949	42.4	664	35.0	1285	47.5	
II	1493	32.4	358	18.9	1135	42.0	
Lymphovascular invasion							0.012
None	2481	53.9	1072	56.5	1409	52.1	
Present	1787	38.8	696	36.7	1091	40.3	
Unknown	334	7.3	129	6.8	205	7.6	
Year							<0.001
2010	997	21.7	355	18.7	642	23.7	
2011	1107	24.1	433	22.8	674	24.9	
2012	1231	26.7	524	27.6	707	26.1	
2013	1266	27.5	584	30.8	682	25.2	
Insurance							<0.001
Uninsured	152	3.3	45	2.8	107	4.0	
Private	1888	41.0	829	43.7	1059	39.1	
Medicaid	212	4.6	65	3.4	147	5.4	
Medicare	2235	48.6	915	48.2	1320	48.8	
Other	106	2.3	34	1.8	72	2.7	
Education							<0.001
≥21%	726	15.8	251	13.2	475	17.6	
13–20.9%	1104	24.0	410	21.6	694	25.7	
7–12.9%	1641	35.7	689	36.3	952	35.2	
<7%	1123	24.4	544	28.7	579	21.4	
Unknown	8	0.2	3	0.2	5	0.2	
Census							<0.001
South	1270	27.6	441	23.2	829	30.6	
Northeast	1248	27.1	620	32.7	628	23.2	
Midwest	1421	30.9	557	29.4	864	31.9	
West	623	13.5	268	14.1	355	13.1	
Unknown	40	0.9	11	0.6	29	1.1	
Facility							<0.001
Community Cancer Program	265	5.8	53	2.8	212	7.9	
Comprehensive Community Cancer Program	1743	37.9	591	31.3	1152	43.0	
Academic/Research	1991	43.3	1007	53.4	984	36.8	
Integrated Network Cancer Program	563	12.2	235	12.5	328	12.3	
Race							0.004
White	3905	84.9	1571	82.8	2334	86.3	
Black	498	10.8	241	12.7	257	9.5	
Other	160	3.5	71	3.7	89	3.3	
Unknown	39	0.8	14	0.7	25	0.9	
Lymph nodes							<0.001
Dissected	3713	80.7	1726	91.0	1987	73.5	
Undissected	889	19.3	171	9.0	718	26.5	

in PORTEC-2 [9]. In some patients at higher risk for pelvic failure, such as those with deep myometrial invasion together with high-grade disease, external beam radiation therapy has been considered standard [2]. However, WPRT is associated with greater toxicity compared to VBT alone [10].

A recently published Gynecologic Oncology Group study (GOG 249) sought to incorporate adjuvant chemotherapy to address pelvic and distant sites of failure while using VBT to reduce local failures at the vaginal cuff. This study randomized HIR patients to vaginal cuff brachytherapy with 3 cycles of paclitaxel and carboplatin vs. whole pelvic radiation therapy with or without a brachytherapy boost. HIR was defined as patients with stage I endometrioid carcinoma and at least one risk factor if age ≥70, at least two risk factors if age 50–69 years old, three high-risk factors at any age, or any stage II disease. Risk factors included the presence of lymphovascular space invasion (LVSI), histologic grade 2–3, or invasion into the outer half of the myometrium. Patients with stage I-II serous or clear cell carcinoma were also included. Final analysis demonstrated an increase in acute toxicity and pelvic failures in the VBT + CT arm, with no difference in distant metastasis rate, progression-free survival, or overall survival [11]. The conclusion of the study was that WPRT alone is an appropriate therapy for the study population. However, this trial included a heterogeneous population in terms of histologic subtype and risk factors, and questions remain regarding the use of chemotherapy in patients with early-stage disease who are at a higher risk of recurrence.

We sought to describe patterns of care and to compare outcomes for patients in a large, retrospective hospital-based registry who met eligibility criteria and received one of the two treatment regimens randomized in GOG 249. Specifically, we sought to identify subsets of patients who may benefit from the addition of chemotherapy vs. radiation directed to pelvic lymph nodes based on clinicopathologic risk features, such as those with serous and clear cell histologic subtypes who were under-represented in GOG 249.

2. Methods

Patients from the National Cancer Database (NCDB) with uterine carcinoma diagnosed from 2010-2013 and fulfilling GOG 249 eligibility criteria were identified (Fig. 1). The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a database of hospital registry data collected from Commission on Cancer-accredited facilities, representing nearly three-quarters of newly diagnosed cancers in the United States. GOG 249 criteria include patients with stage I endometrioid carcinoma and at least one risk factor if age ≥70, at least two risk factors if age 50–69 years old, three high-risk factors at any age, or any stage II disease. Risk factors considered are the presence of lymphovascular space invasion (LVSI), histologic grade 2–3, or invasion into the outer half of the myometrium. In addition, patients with stage I-II serous or clear cell carcinoma were also included. Just as in GOG 249, carcinosarcoma histology was excluded. Patients who received VBT with chemotherapy or WPRT alone were included. Those undergoing observation or chemotherapy (CT) alone were excluded, given the potential for

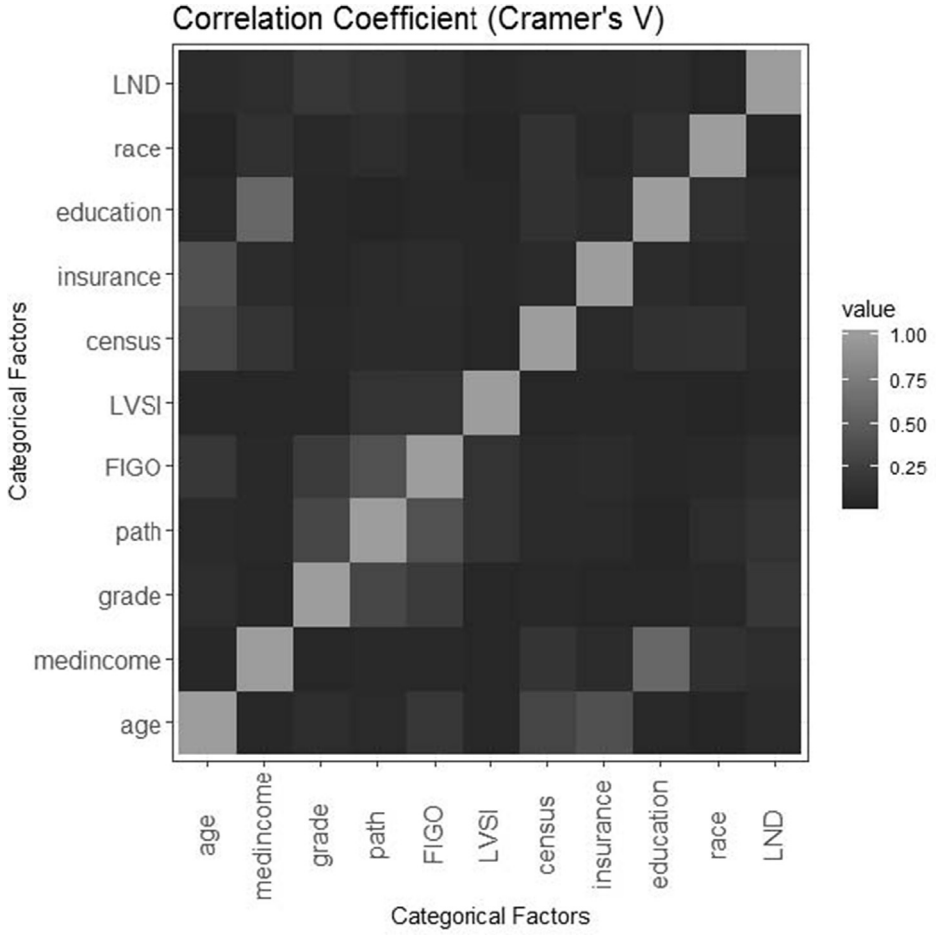

Fig. 2. Correlation map between the risk factors included in the multivariate analysis. Age was examined as groups based on the three age categories described earlier with boundaries at 50 and 70 years of age. Census describes location throughout the country as subdivided into 4 groups: south, northeast, midwest, and west.

significant selection bias due to underlying comorbidity or poor performance status. All patients were staged using 7th edition AJCC staging. Those staged with prior edition AJCC staging were excluded.

Univariate analysis was performed by log-rank testing to assess the association of individual factors with overall survival (OS). Those parameters not significant on univariate testing ($p \geq 0.05$), were excluded from later multivariable examination. In addition, correlations between variables were also examined prior to multivariate analysis in order to identify any dependencies, which may confound results on multivariable analysis.

Multivariable analysis was performed using the Cox regression analysis to evaluate outcomes by treatment (VBT + CT vs. EBRT with or without VBT boost), for the cohort of patients that would have qualified for GOG 249. In addition, overall outcomes by histology were examined. Finally, multiple subsets of patients were examined to evaluate association of treatment with survival. Subgroups examined include those with high-grade endometrioid histology, high-risk histology, the presence of LVSI, and the use of lymph node dissection. Where appropriate, combinations of high risk factors were also examined to determine if a specific treatment was associated with improved outcome in specific subsets of patients.

3. Results

A total of 4,602 patients were included in the analysis (N = 1,897 VBT + CT, N = 2,705 EBRT ± VBT). Median follow-up time was 34 months. Patient characteristics overall and by treatment group are detailed in Table 1.

Factors that appreciably varied between the treatment groups included histology, grade, FIGO stage, year of treatment, type of facility, and the presence of a lymph node dissection. High-grade carcinomas tended to make up a larger fraction of those undergoing chemotherapy containing treatment, while higher FIGO stage made up a greater proportion of EBRT treated patients. A greater proportion of VBT + CT occurred at academic centers, with increasing brachytherapy use in more recent years. Of those treated with brachytherapy, 91% had a lymph node dissection, while only 74% of those receiving EBRT had undergone a lymph node dissection ($p < 0.001$).

3-year OS for the entire cohort was 86%. By treatment, overall survival at 3 years was 89.6% and 87.8% for VBT + CT and EBRT, respectively ($p = 0.44$). Five-year OS was 78.1% vs. 76.7% ($p = 0.17$). By histology, overall survival was 89% for endometrioid, 87% for serous, and 88% for clear cell carcinomas ($p = 0.44$). Five-year OS was 79.3%, 69.9%, and 73.9%, respectively ($p = 0.028$).

Univariate analysis demonstrated multiple factors that were associated with survival: age, grade, histology, FIGO stage, LVSI, comorbidity index, histology, insurance, race, and pathologic nodal evaluation (all $p < 0.05$). The facility type, year of treatment, distance traveled for treatment, and type of treatment received were not statistically significant predictors for survival.

Many variables demonstrated correlation; Cramer's V values [12] for each pair of variables are plotted in Fig. 2. Education was correlated with several other social factors, such as age and income, but was not correlated with the pathologic features of the tumor.

Results of the multivariable analysis (Table 2) revealed factors independently associated with worse survival. Among these, the greatest hazard ratio (HR) was for high grade disease, with undifferentiated histology having HR 3.56 (95% CI: 2.22–5.60, $p < 0.001$), and age, with those over 70 years old having a HR 3.02 (95% CI: 1.68–5.45, $p < 0.001$). Other factors associated with poor survival included LVSI (HR 1.61; 95% CI 1.325–1.92, $p < 0.001$), serous histology (HR 1.60; 95% CI 1.25–2.05, $p < 0.001$), and black race (HR 1.38; 95% CI: 1.09–1.74, $p = 0.008$). Finally, treatment with EBRT as compared to VBT + CT was significantly associated with worse OS (HR 1.24; 95% CI 1.01–1.52, $p = 0.043$).

Subset analysis was performed to evaluate whether the survival benefit associated with VBT + CT was limited to specific populations (Fig. 3). High-risk groups examined included high-grade endometrioid carcinoma, serous carcinoma, clear cell carcinoma, and those without lymph node dissection. Among these groups, only serous carcinoma patients demonstrated a significantly increased HR for death when treated with EBRT alone (N = 1,002; HR 1.76, 95% CI: 1.18–2.64, $p = 0.006$). Those patients with endometrioid histology but no lymph node dissection appeared to have a numerically improved survival associated with EBRT, with this effect becoming more significant in the presence of additional high-risk features, such as LVSI or high grade (grade 3).

On subset analysis, the survival benefit associated with the addition of chemotherapy appears to be limited to primarily the serous histology patients. The degree of this survival benefit is substantial, as seen in the Kaplan-Meier plot in Fig. 4. Multivariable analysis excluding serous carcinoma revealed no association of treatment type with survival (data not shown). Similarly, there was no difference in survival by treatment type for those with clear cell histology.

4. Discussion

In this large hospital-based registry study, VBT + CT was independently associated with improved survival compared to EBRT, but this benefit appeared to be limited to serous carcinoma patients. For non-serous histology patients, the results presented here appear to be in agreement with the overall results of GOG 249, demonstrating no difference in survival by treatment type.

Table 2
Multivariable analysis of overall survival for high-intermediate and high-risk endometrioid carcinoma patients.

Characteristic	HR	95% CI	P-value
Treatment (ref: vaginal brachytherapy and chemotherapy)			
External beam radiation	1.239	1.007–1.524	0.043
Age (ref: <50 y)			
50-69	1.568	0.889–2.767	0.121
≥70 y	3.022	1.676–5.450	<0.001
Lymphovascular invasion (ref: absent)			
Present	1.610	1.351–1.920	<0.001
Unknown	1.357	0.976–1.887	0.070
Grade (ref: well-differentiated)			
Moderately differentiated	1.687	1.178–2.419	0.004
Poorly differentiated	3.289	2.318–4.668	<0.001
Undifferentiated	3.527	2.221–5.601	<0.001
Unknown	2.089	1.403–3.110	<0.001
Charlson Comorbidity Index (ref: 0)			
1	1.168	0.958–1.426	0.125
2	1.455	1.053–2.012	0.023
Pathologic nodal status (ref: pN0)			
pNx	1.694	1.393–2.060	<0.001
Histology (ref: endometrioid)			
Serous	1.599	1.249–2.047	<0.001
Clear cell	1.125	0.726–1.742	0.598
Race (ref: white)			
Black	1.377	1.088–1.742	0.008
Other	0.758	0.426–1.349	0.346
Unknown	0.751	0.280–2.013	0.569
Insurance (ref: uninsured)			
Private	1.124	0.608–2.075	0.710
Medicaid	1.503	0.735–3.072	0.264
Medicare	1.408	0.758–2.616	0.279
Other	1.084	0.458–2.566	0.855
FIGO Stage (ref: IA)			
I	1.684	0.617–4.600	0.309
IB	1.918	1.494–2.462	<0.001
II	2.285	1.757–2.971	<0.001

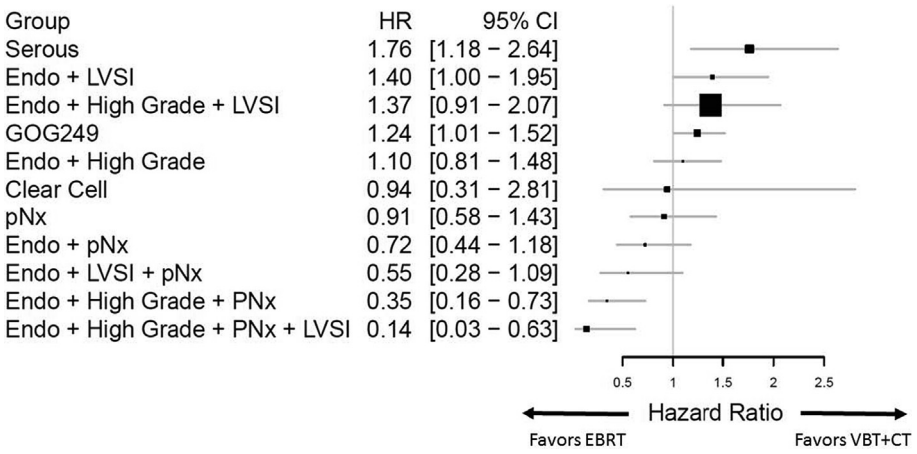

Fig. 3. Plot of 95% confidence interval for the hazard ratio of EBRT vs VBT + CT. "GOG 249" indicates all patients included in this analysis. "Endo" = endometrioid histology, LVSI = lymphovascular space invasion.

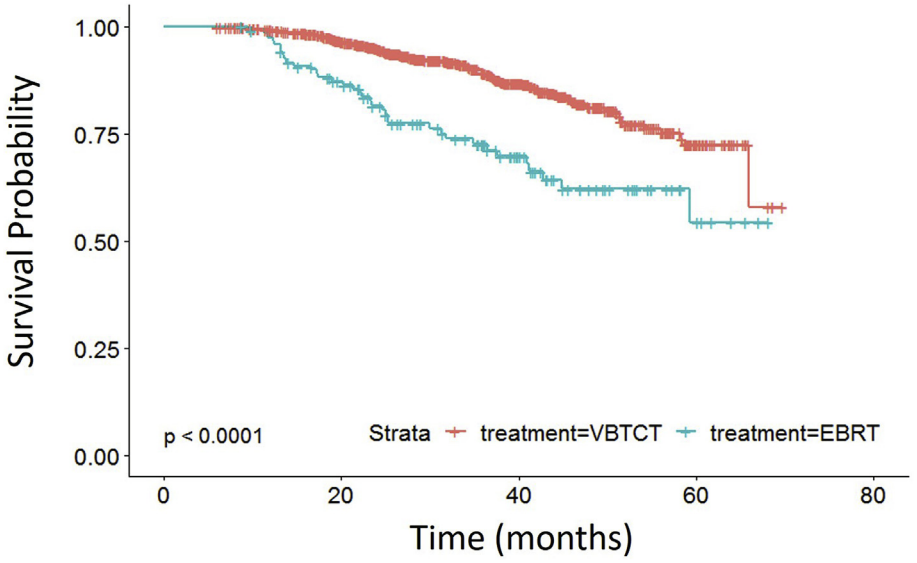

Fig. 4. Kaplan-Meier estimate of overall survival for serous carcinoma patients by treatment type. VBTCT = vaginal brachytherapy and chemotherapy. EBRT = External beam radiation therapy.

However, the present analysis includes a greater proportion of serous histology patients (22% compared to 14.6% in GOG 249), and treatment type was associated with survival in this subset, while in GOG 249 there was no difference observed in the combined serous and clear cell patients. This may be attributable to differences in patient numbers, with >1,000 serous histology patients in this analysis compared to only 88 in GOG 249 [11]. The grouping of clear cell patients together with serous histology in the GOG 249 analysis may have also reduced the perceived benefit of chemotherapy. The finding here that clear cell histology does not benefit from the addition of chemotherapy is consistent with prior NCDB analyses [13]. No additional non-serous sub-groups of patients were found to benefit from VBT + CT. This is consistent with results of the PORTEC-3 analysis, as the benefit of chemotherapy to EBRT was not observed in the subset of stage I-II high-risk patients [14].

In our study, EBRT was associated with superior survival when compared to VBT + CT specifically in high-grade patients without nodal dissection. The presence of LVSI in those with high-grade disease and no nodal dissection seems to further favor EBRT. LVSI has been associated with an increased risk of nodal metastases as well as an increased risk of locoregional and distant relapse [17,18]. However, its prognostic value may be limited after controlling for lymph node metastases and other associated risk factors [19]. To date, there has been no clearly demonstrated therapeutic benefit to lymph node dissection [15,16], but the resulting pathologic nodal staging is important in determining adjuvant therapy. Adjuvant radiotherapy has demonstrated improved locoregional control in FIGO IIIC patients [20] and it is reasonable to anticipate that EBRT (rather than vaginal cuff brachytherapy) may benefit those early stage patients at higher risk for pelvic recurrence as well [21]. Indeed, in GOG 249, patterns of failure data demonstrate higher rates of nodal relapse in the VBT + CT arm, despite 89.4% of patients having undergone lymphadenectomy [11]. This is counter to PORTEC-2 data in which nodal dissection was not mandated and risk of pelvic metastases was very low with vaginal brachytherapy only [9]; however, sampling of abnormal appearing lymphadenopathy was performed and patients in PORTEC-2 were overall lower risk, with approximately only 10% of patients having LVSI and about 8% having grade 3 disease on central pathology review [6]. Taken together, these findings suggest that patients with worse risk features such as LVSI and/or high-grade disease may benefit from lymph node dissection to inform appropriate adjuvant therapy. In

those who are unable to undergo dissection, EBRT may be important, as chemotherapy with vaginal brachytherapy may be insufficient to address potential occult nodal disease. The practice patterns analyzed in this study demonstrate a similar approach, with the number of patients without nodal dissection being significantly greater in the EBRT population (26.5%) vs the VBT + CT population (9.0%).

Limitations of this study include the retrospective nature of the data with its associated biases, as well as potential error in data collection. There is most certainly selection bias associated with the use of chemotherapy, such as avoidance in those who were felt to be too frail to tolerate it. Further, it is difficult to make complete comparisons to the randomized data in the literature as many of the clinical outcome measures, such as progression free survival or patterns of failure, are not available in this dataset. Consequently, it was not possible to examine the primary outcome measure of recurrence free survival as was done in GOG 249. Rather, overall survival (a secondary endpoint in GOG 249) was examined. Similarly, toxicity data are also lacking in these data which may play in important role in clinical decision making and result in further patient selection that cannot be accounted for in these analyses. Finally, many of the details of the radiotherapy prescriptions, as well as number of cycles and type of chemotherapy used, are also not present in these data.

The use of EBRT or VBT + CT is a reasonable treatment strategy in most early-stage HIR endometrial cancers. A notable exception to this may be those with serous histology, where chemotherapy could be beneficial in combination with radiation. Additionally, those with multiple high-risk features (especially LVSI) in the absence of lymph node dissection may benefit from external beam radiation directed to the whole pelvis regardless of the use of chemotherapy. Further optimization of systemic therapy regimens and improved patient selection using molecular and/or clinicopathologic risk features may identify those who would benefit most from chemotherapy in the future.

Author contributions

KT: formal analysis, methodology, writing – original draft.
YH: writing – review & editing.
CHS: conceptualization, data curation, methodology, formal analysis, supervision, writing – review & editing.

Declaration of competing interest

The authors do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.09.028.

References

[1] C.P. Morrow, B.N. Bundy, R.J. Kurdman, et al., Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium, Gynecol. Oncol. 40 (1991) 55–65.
[2] J. Aalders, V. Abeler, P. Kolstad, M. Onsrud, Postoperative external Irradiation and prognostic parameters in stage I endometrial carcinoma, Obstet. Gynecol. 56 (4) (1980) 419–427.
[3] T. Bosse, E.E.M. Peters, C.L. Creutzberg, et al., Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer, Eur. J. Cancer 51 (2015) 1742–1750.
[4] A.N. Viswanathan, E.A. Macklin, R. Berkowitz, U. Matulonis, The importance of chemotherapy and radiation in uterine papillary serous carcinoma, Gynecol. Oncol. 123 (2011) 542–547.
[5] C.L. Creutzberg, R.A. Nout, M.L.M. Lybeert, et al., Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trail for endometrial carcinoma, IJROBP 81 (4) (2011) e631–e638.
[6] B.G. Wortman, C.L. Creutzberg, H. Putter, et al., Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma, Br. J. Canc. 119 (2018) 1067–1074.
[7] H.M. Keys, J.A. Roberts, V.L. Brunetto, et al., A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma, Gynecol. Oncol. 92 (3) (2004) 744–751.
[8] C.L. Creutzberg, W.L.J. van Putten, P.C.M. Koper, et al., Surgery and post-operative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma, Lancet 355 (2000) 1404–1411.
[9] R.A. Nout, V.T.H.B.M. Smith, H. Putter, et al., Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2), Lancet 375 (9717) (2010) 816–823.
[10] R.A. Nout, H. Putter, I.M. Jurgenliemk-Schulz, et al., Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer, J. Clin. Oncol. 27 (21) (2009) 3547–3556.
[11] M.E. Randall, V. Filiaci, D.S. McMeekin, et al., Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer, J. Clin. Oncol. 18 (2019), 01575. JCO.
[12] H. Cramer, Mathematical Methods of Statistics, Princeton University Press, Princeton, NJ, 1946.
[13] K. Nieto, W. Adams, N. Pham, et al., Adjuvant therapy in patients with clear cell endometrial carcinoma, Gynecol. Oncol. 148 (1) (2018) 147–153.
[14] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3), Lancet Oncol. 19 (2018) 295–309.
[15] H. Kitchener, P. Blake, J. Sandercock, et al., Efficacy of systemic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial), Lancet 373 (9658) (2009) 125–136.
[16] P.B. Panici, S. Basile, F. Manesci, et al., Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma, J. Natl. Cancer Inst. 100 (23) (2008) 1707–1716.
[17] S.R. Guntupalli, I. Zighelboim, N.T. Kizer, et al., Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer, Gynecol. Oncol. 142 (2012) 31–35.
[18] J.M. Briët, H. Hollema, N. Reesink, et al., Lymphvascular space involvement: an independent prognostic factor in endometrial cancer, Gynecol. Oncol. 96 (3) (2005) 799–804.
[19] S.A. Neal, W.S. Graybill, E. Garrett-Mayer, et al., Lymphovascular space invasion in uterine corpus cancer, Gynecol. Oncol. 142 (2) (2016) 278–282.
[20] D. Matei, V.L. Filiaci, M. Randall, et al., A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma, J. Clin. Oncol. 35 (15) (2017), 5505-5505.
[21] A. Kong, N. Johnson, H.C. Kitchener, T.A. Lawrie, Adjuvant Radiotherapy for Stage I Endometrial Cancer: an Updated Cochrane Systematic Review and Meta-Analysis, vol. 104, 2012, pp. 1625–1634, 21.