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Adjuvant radiation therapy and health-related quality of life among older women with early-stage endometrial cancer: an analysis using the SEER-MHOS linkage

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Abstract

Purpose Radiation therapy (RT) has been associated with decreased health-related quality of life (HRQOL) in clinical trials of early-stage endometrial cancer (EC), but few studies have examined the association in real-world settings. We assessed HRQOL associated with adjuvant RT for older women with early-stage EC within a large U.S. population-based registry resource.

Methods The Surveillance Epidemiology and End Results and the Medicare Health Outcomes Survey linkage (1998–2017) was used to identify women with early-stage EC aged ≥ 65 years at survey who received surgery and were diagnosed ≥ 1-year prior ($n = 1{,}140$). HRQOL was evaluated with the 36-item Short-Form Health Survey (SF-36) until 2006 and the Veterans RAND 12-Item Health Survey (VR-12) post 2006. Ordinary least squares regression was used to estimate mean difference (MD) in *T* scores and 95% confidence intervals (CIs) comparing treatment groups (surgery alone, adjuvant external beam radiation therapy [EBRT], or adjuvant vaginal brachytherapy [VBT]) after accounting for confounders using propensity score weighting.

Results Overall, RT was not associated with physical health (MD = 0.97; 95% CI = − 1.13, 3.07) or mental health (MD = − 0.78; 95% CI = − 2.60, 1.05) relative to surgery alone. In analyses by RT type, adjuvant VBT was associated with better general health on the SF-36/VR-12 subscale (MD = 3.59; 95% CI = 0.56, 6.62) relative to surgery alone. No statistically significant associations were observed for adjuvant VBT and physical or mental health, or for adjuvant EBRT and any HRQOL domain.

Conclusion Older women with early-stage EC treated with adjuvant RT did not report worse physical and mental HRQOL scores compared to those treated with surgery alone, though relevant symptoms should be evaluated further to fully understand the disease and treatment specific aspects of the HRQOL.

Keywords Quality of life · Brachytherapy · Adjuvant radiotherapy · Endometrial neoplasms

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Introduction

Endometrial cancer (EC) is the fourth most common cancer among American women and its incidence and mortality rates continue to rise [1]. In 2021, an estimated 66,570 new ECs will be diagnosed and 12,940 women will die of this disease [2]. EC is also a cancer of older women, with a median age of 63 years at diagnosis [1, 3] and nearly 45% of women diagnosed are age 65 or older [3]. Projections indicate that EC burden in the U.S. will continue to rise over the next decade due to the ongoing epidemic in obesity, a major EC risk factor, and an aging population [4, 5].

Most EC patients are diagnosed at an early-stage (67% of diagnoses) [3], and the majority require only surgical intervention [6]. Adjuvant radiation therapy (RT) is an essential component of treatment in early-stage EC with high risk of recurrence, even though the benefits of RT in early-stage patients remain unclear [7]. Clinical trials have shown that adjuvant RT does not improve overall survival but does reduce the risk of central recurrence at the cost of side effects that affect patients' health-related quality of life (HRQOL) [8–11]. Of the two commonly administered forms of RT for EC, vaginal brachytherapy (VBT) has been associated with more favorable HRQOL profile compared to external beam radiation therapy (EBRT) [12].

National guidelines recommend RT to be offered to older patients based on evaluation of the benefits and risks associated with the treatment, with consideration of the patient's underlying functional reserve and responsiveness to therapy [13]. However, evidence specific for older women with early-stage EC and HRQOL associated with RT has been largely lacking. Therefore, in this study, we aimed to assess HRQOL outcomes associated with adjuvant RT for older women with early-stage EC within a large U.S. national population-based registry resource. Among older women with early-stage EC who underwent primary surgical intervention, the objectives of this study were (1) to evaluate whether adjuvant RT negatively affects patients' HRQOL and (2) to compare HRQOL outcomes according to adjuvant RT type (VBT or EBRT).

Methods

Data source and study population

We utilized data from a linkage of the Surveillance Epidemiology and End Results (SEER) cancer registry program and the Medicare Health Outcomes Survey (MHOS) [14, 15]. The SEER registries contain approximately 97% of all incident cancer cases from tumor registries in 19 U.S. geographic areas that cover 34.6% of the U.S. population [16, 17]. The information collected by SEER includes demographics, diagnosis dates, tumor characteristics, surgical treatment and RT recommended or provided as first course of treatment, follow-up of vital status, and cause of death. The MHOS measures health outcomes of Medicare beneficiaries enrolled in Medicare Advantage health plans [15]. The core MHOS survey contains questions on demographics, socioeconomic status, health problems, functional status, and symptoms. The detailed MHOS survey design has been described elsewhere [15]. We used the SEER-MHOS dataset linking beneficiaries who were respondents to the MHOS from 1998 to 2017 to SEER data from 1988 to 2015. The study was determined to be exempted from full review by the Institutional Review Board at the University of North Carolina at Chapel Hill.

The SEER-MHOS dataset included 5,305 women diagnosed with EC during 1988–2015. Women aged ≥ 65 years with a pathologic confirmed diagnosis of first primary AJCC stage I–II EC who underwent a primary surgery and completed at least one MHOS survey ≥ 1-year post-diagnosis were eligible for inclusion ($n = 1{,}440$) (Fig. 1). Women were excluded if they had received any neoadjuvant RT or had incomplete data on RT ($n = 27$). Women with incomplete data on HRQOL ($n = 80$) or confounders ($n = 193$) were also excluded. In total, 1,140 women were included in the analysis.

Adjuvant RT measures

Adjuvant RT receipt was identified via SEER registry treatment fields. The variable has been shown to have a high level of agreement with RT claims captured via Medicare sources (inpatient, outpatient and physician/supplier files for the 9-month period after diagnoses) [18]. Adjuvant RT type was stratified into two categories: VBT or EBRT. Women treated with both VBT and EBRT were not included in the analyses by RT type.

HRQOL measures

On the MHOS, HRQOL was measured using the 36-item Short-Form Health Survey (SF-36) through 2005. To improve performance of the SF-36 in patient populations with poor health, it was reduced from 36 to 12 items, resulted in the use of the Veterans RAND 12-Item Health Survey (VR-12) for 2006 and later [19]. Published bridge algorithms were used to re-score the eight scale scores (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Mental Health, Role-Emotional, Social Functioning) to make the VR-12 comparable to the SF-36 [19, 20]. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were calculated based on eight scale scores. The PCS and MCS scores have been

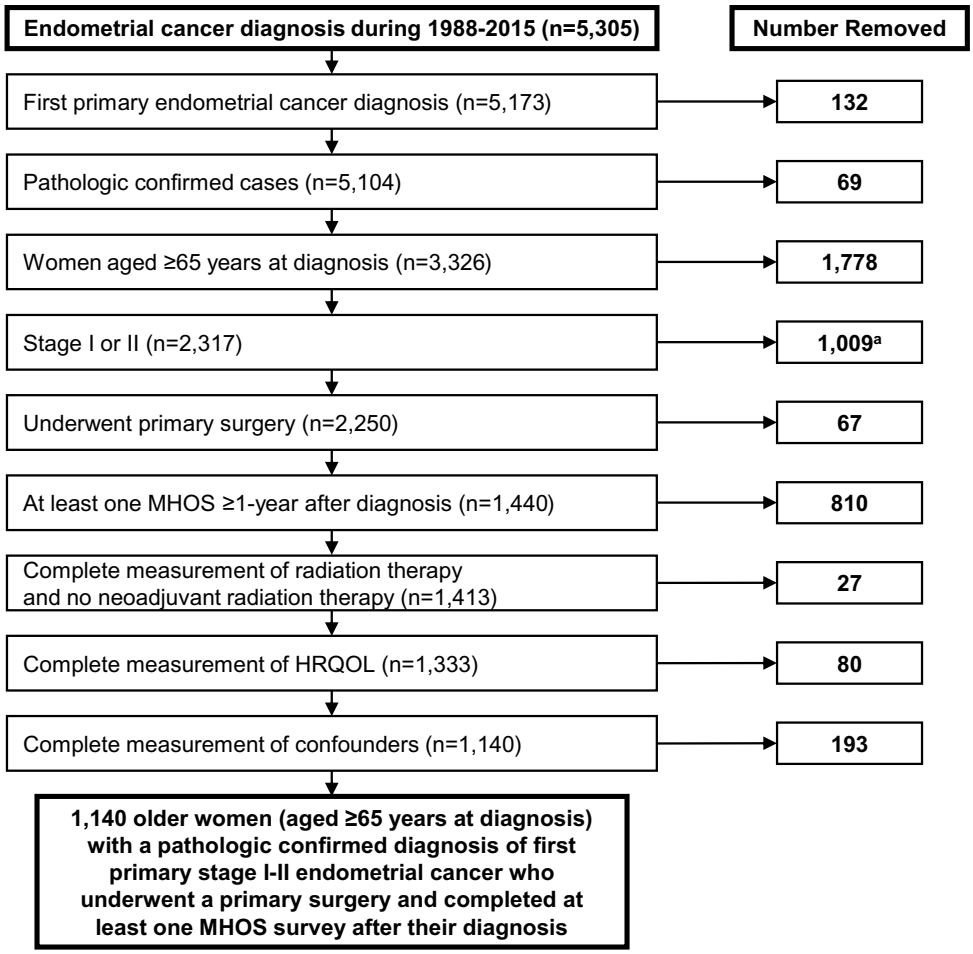

Fig. 1 Flow diagram shows selection of study cohort. [a]Excluded individuals diagnosed with in situ ($n=41$) or advanced disease (stage III [$n=311$] or IV [$n=165$]), or unknown stage information ($n=492$). *MHOS* Medicare health outcomes survey, *HRQOL* Health-related quality of life

normalized to the 1990 U.S. general population and rescored on a *T* score metric (range 0–100; mean ± SD, 50 ± 10; higher scores reflect better HRQOL). If a woman completed more than one survey, the survey closest to 1-year post-diagnosis date was selected.

Covariates

Characteristics including race/ethnicity, marital status, education level, activities of daily living (ADL), comorbidities, and body mass index (BMI) were assessed using the closest MHOS completed ≥ 1-year post-diagnosis. Katz's basic ADL collected on MHOS included walking, dressing, bathing, getting in/out of chairs, eating, and toileting. Each item was measured with the following question: "Because of a health or physical problem, do you have any difficulty doing the following activities without special equipment or help from another person?" We also dichotomized responses for ADL as either limited (have difficulty/unable to do activity) or not limited (no difficulty) [21]. Self-reported comorbidities collected on MHOS included cardiovascular conditions (angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, or stroke); hypertension; gastrointestinal conditions (Crohn's disease, ulcerative colitis, or inflammatory bowel disease); musculoskeletal conditions (arthritis of the hand/wrist, arthritis of the hip/knee, sciatica, or osteoporosis); respiratory conditions (emphysema, asthma, or COPD); and diabetes.

Cancer-specific characteristics including age at diagnosis, year at diagnosis, tumor stage, grade, histologic subtype, and lymph node assessment were identified from SEER. Consistent with prior research [22], using the International Classification of Diseases for Oncology (ICD-O-3) histology codes, we classified the histology into three categories: 'Type I, endometrioid tumors', 'Type II, non-endometrioid tumors', or 'Other, unclassifiable tumors'.

Statistical analysis

Descriptive statistics were used to summarize demographics and clinical characteristic variables for the entire cohort and by adjuvant RT receipt and RT modality. To examine the association between adjuvant RT and HRQOL, we first compared the *T* scores of the women treated with adjuvant RT vs surgery alone. We then compared the *T* scores by adjuvant

RT type: (1) adjuvant EBRT vs surgery alone; (2) adjuvant VBT vs surgery alone. To account for measured confounding, we performed propensity score analysis with standardized mortality ratio (SMR) weighting [23]. We fitted three logistic regression models to estimate the conditional probability of receiving each treatment for each women using both confounders and independent risk factors for the HRQOL [24]. Confounders included age at diagnosis, time from diagnosis to survey, diagnosis year, race/ethnicity, marital status, education level, stage, grade, histologic subtype, lymph node assessment, comorbidities, and difficulty with ADL. Women in the index treatment group were given a weight one, while weights for women in the referent treatment group were defined as the ratio of the estimated propensity score to one minus the estimated propensity score [25, 26]. To reduce variability due to instability in estimation that could be induced by women with very large weights, weights were stabilized by multiplying the previously defined weights by the marginal probability of not receiving treatment and the reciprocal of the marginal probability of receiving treatment for those not treated. We assessed covariate balance across treatment groups by calculating the standardized mean difference for each covariate [27].

To compare the *T* scores between treatment groups, we estimated crude and weighted means and 95% confidence intervals (CIs) using ordinary least square models with robust standard errors [28]. Differences in crude and weighted means of treatment groups and corresponding 95% CIs were also calculated.

In sensitivity analyses restricted to MHOS from 2006 to 2017, we further controlled for potential confounding by BMI in propensity score models to assess whether the inclusion of BMI in the model altered the estimates of differences in marginal means in HRQOL *T* scores.

Results

A total of 1,140 women with a diagnosis of first primary stage I–II EC were included. The median age at diagnosis was 71 years (IQR: 67, 76) (Table1); median time from diagnosis to survey was 5.2 years (IQR: 2.8–9.3); majority of women were non-Hispanic White (81%) and had at least a high school education (80%); 35% were married at the time of survey. Most women had stage I disease (93%), grade 1 or 2 (84%), and endometrioid histology (90%), and less than half received lymph node assessment (48%). At the time of survey, 68% were overweight or obese. Hypertension (68%), diabetes (66%), and cardiovascular conditions (35%) were the most common comorbidities. The most common difficulties with ADL was difficulty with walking (42%) and difficulty with getting in/out of a chair (31%).

In our sample, 24% received any form of adjuvant RT. Women treated with adjuvant RT were more likely to have tumors with higher stage and grade, and more likely to receive lymph node assessment than women treated with surgery alone. Cardiovascular conditions were more commonly reported in women treated with surgery alone than women treated with adjuvant RT (37 vs 28%). No other material differences in distribution of demographics were observed between women treated with surgery alone vs adjuvant RT.

Crude mean scores for the physical and mental HRQOL of women with early-stage EC were 36.16 (95% CI 36.01–37.40) and 51.97 (95% CI 51.30–52.63), respectively, which indicated lower physical and mental HRQOL than the US general population (mean *T* score; physical = 45.55 and mental = 54.62 for women aged 65–74 years, and physical = 42.65 and mental = 54.39 for women aged 75–89 years) [29] After weighting, the magnitude of the standardized mean differences of the patient characteristics across treatment groups was significantly reduced, indicating improved confounding control (Supporting Figs. 1–3).

Overall, no substantial differences in mean *T* scores according to RT receipt were observed for physical (mean difference, 0.97; 95% CI − 1.13–3.07) and mental health (mean difference, − 0.78; 95% CI − 2.60–1.05) (Table2). When HRQOL was further analyzed according to subscale, we observed no statistically significant differences in mean *T* scores according to adjuvant RT receipt for all eight subscales. In sensitivity analyses restricted to records from 2006 to 2017, further adjustment for BMI did not meaningfully alter the estimates for physical (mean difference, 1.06; 95% CI − 1.32–3.45) and mental health (mean difference, − 1.30; 95% CI − 3.65–1.04) relative to the estimates without the adjustment of BMI (mean difference for physical and mental health was 0.79; 95% CI − 1.70–3.29 and − 0.94; 95% CI − 3.29–1.41, respectively).

Among women who received RT after surgery, 155 received adjuvant EBRT and 67 received adjuvant VBT. The distribution of demographic and clinical characteristics by adjuvant RT type are shown in Supporting Table 1. No statistically significant associations were observed for adjuvant EBRT and HRQOL component summary *T* scores (Fig. 2). In analyses of eight subscales, the mean *T* score for role-emotional functioning was lower for women treated with adjuvant EBBT vs surgery alone (mean difference, − 2.14; 95% CI − 4.53–0.25), however were not statistically significant. Likewise, no statistically significant associations were observed for adjuvant VBT and HRQOL component summary *T* scores. However, in analyses of eight subscales, the mean *T* score for general health functioning was statistically significantly higher for women treated with adjuvant VBT vs surgery alone (mean difference, 3.59; 95% CI 0.56–6.62).

Table 1 Demographics and clinical characteristics of older women diagnosed with stage I-II endometrial cancer during 1988–2015, overall and stratified by adjuvant radiation therapy receipt

Characteristics	Overall ($n=1,140$)		Adjuvant RT ($n=276$)		Surgery alone ($n=864$)	
	N	(%)	*N*	(%)	*N*	(%)
Age at diagnosis, years, median (SD), IQR	71 (5.7), 67–76		70 (5.3), 67–75		71 (5.8), 67–76	
Time from diagnosis to survey, Median (SD), IQR	5.2 (4.6), 2.8–9.3		4.7 (4.4), 2.4–8.5		5.4 (4.7), 2.8–9.6	
1–3 years	345	(30)	93	(34)	252	(29)
3–5 years	215	(19)	55	(20)	160	(19)
5–10 years	343	(30)	81	(29)	262	(30)
> 10 years	237	(21)	47	(17)	190	(22)
Year of diagnosis						
1988–1999	507	(44)	126	(46)	381	(44)
2000–2009	511	(45)	120	(43)	391	(45)
2010–2015	122	(11)	30	(11)	92	(11)
Race/Ethnicity						
Non-Hispanic white	929	(81)	224	(81)	705	(82)
Non-Hispanic black	57	(5)	13	(5)	44	(5)
Hispanic	66	(6)	19	(7)	47	(5)
Other[a]	88	(8)	20	(7)	68	(8)
Marital status						
Married	400	(35)	100	(36)	300	(35)
Separated, divorced, or widowed	683	(60)	164	(59)	519	(60)
Never married	57	(5)	12	(4)	45	(5)
Education level						
Less than high school	230	(20)	63	(23)	167	(19)
High school graduate or GED	424	(37)	107	(39)	317	(37)
Associate's degree/some college	311	(27)	61	(22)	250	(29)
Bachelor's degree or higher	175	(15)	45	(16)	130	(15)
AJCC stage						
IA	394	(35)	75	(27)	319	(37)
IB	87	(8)	45	(16)	42	(5)
I NOS	575	(50)	110	(40)	465	(54)
II	84	(7)	46	(17)	38	(4)
Tumor grade						
G1, Well differentiated	550	(48)	74	(27)	476	(55)
G2, Moderately differentiated	407	(36)	117	(42)	290	(34)
G3 or G4, Poorly differentiated or Undifferentiated/ anaplastic	183	(16)	85	(31)	98	(11)
Histologic subtype						
Type I (endometrioid type)	1,024	(90)	237	(86)	787	(91)
Type II (non-endometrioid type)	45	(4)	14	(5)	31	(4)
Other	71	(6)	25	(9)	46	(5)
Received lymph node assessment	544	(48)	157	(57)	387	(45)
Comorbidities						
Cardiovascular conditions	397	(35)	77	(28)	320	(37)
Hypertension	772	(68)	188	(68)	584	(68)
Respiratory conditions	131	(11)	32	(12)	99	(11)
Musculoskeletal conditions	67	(6)	22	(8)	45	(5)
Diabetes	756	(66)	186	(67)	570	(66)
Gastrointestinal conditions	270	(24)	59	(21)	211	(24)
Difficulty with activities of daily living						
Bathing	219	(19)	55	(20)	164	(19)

Table 1 (continued)

Characteristics	Overall ($n=1,140$)		Adjuvant RT ($n=276$)		Surgery alone ($n=864$)	
	N	(%)	*N*	(%)	*N*	(%)
Dressing	159	(14)	36	(13)	123	(14)
Eating	76	(7)	15	(5)	61	(7)
Getting in/out of a chair	348	(31)	74	(27)	274	(32)
Walking	477	(42)	117	(42)	360	(42)
Toilet use	141	(12)	29	(11)	112	(13)
Body Mass Index at survey[b]						
Underweight/Normal (BMI < 25 kg/m^2)	234	(33)	52	(32)	182	(33)
Overweight (BMI 25- < 30 kg/m^2)	190	(27)	36	(22)	154	(28)
Obese (BMI ≥ 30 kg/m^2)	292	(41)	74	(46)	218	(39)

AJCC American joint committee on cancer, *NOS* Not otherwise specified, *G* Grade, *BMI* Body Mass Index, *RT* radiation therapy

[a]Other race includes Asian American and Pacific Islander, American Indian or Alaskan Native, Another race, or multi-race

[b]Analyses restricted to records from 2006 to 2017 with complete data on BMI

Table 2 Crude and weighted means with 95% CIs and differences in crude and weighted means with 95% CIs for SF-36/VR-12 *T* scores of physical and mental HRQOL according to adjuvant radiation therapy receipt

	Crude mean (95% CI)		Differences in crude means (95% CI)	Weighted mean (95% CI)		Differences in weighted means (95% CI)
	Surgery alone ($n=864$)	Adjuvant RT ($n=276$)		Surgery alone ($n=864$)	Adjuvant RT ($n=276$)	
SF-36/VR-12 *T* scores						
Physical component summary	36.54 (35.73, 37.34)	37.22 (35.84, 38.60)	0.68 (− 0.91, 2.28)	36.25 (34.67, 37.83)	37.22 (35.84, 38.60)	0.97 (− 1.13, 3.07)
General health	44.17 (43.42, 44.91)	44.51 (43.24, 45.78)	0.34 (− 1.13, 1.82)	44.28 (42.84, 45.73)	44.51 (43.24, 45.78)	0.23 (− 1.70, 2.15)
Physical functioning	35.53 (34.64, 36.42)	35.86 (34.23, 37.49)	0.33 (− 1.52, 2.19)	35.47 (33.72, 37.21)	35.86 (34.23, 37.49)	0.39 (− 1.99, 2.78)
Role-physical	39.48 (38.65, 40.31)	40.05 (38.60, 41.51)	0.57 (− 1.11, 2.25)	39.42 (37.61, 41.23)	40.05 (38.60, 41.51)	0.63 (− 1.69, 2.96)
Bodily pain	41.73 (40.98, 42.47)	42.38 (41.10, 43.66)	0.65 (− 0.83, 2.14)	41.67 (40.25, 43.08)	42.38 (41.10, 43.66)	0.71 (− 1.20, 2.62)
Mental component summary	52.04 (51.28, 52.79)	51.74 (50.36, 53.12)	− 0.30 (− 1.87, 1.27)	52.52 (51.32, 53.71)	51.74 (50.36, 53.12)	− 0.78 (− 2.60, 1.05)
Role-emotional	46.61 (45.78, 47.43)	45.82 (44.36, 47.28)	− 0.79 (− 2.47, 0.89)	47.37 (46.13, 48.61)	45.82 (44.36, 47.28)	− 1.55 (− 3.47, 0.37)
Vitality	45.44 (44.70, 46.18)	45.58 (44.27, 46.90)	0.15 (− 1.36, 1.65)	45.45 (44.11, 46.79)	45.58 (44.27, 46.90)	0.13 (− 1.74, 2.01)
Mental health	50.47 (49.74, 51.21)	50.96 (49.69, 52.23)	0.48 (− 0.98, 1.95)	50.97 (49.66, 52.27)	50.96 (49.69, 52.23)	− 0.01 (− 1.82, 1.81)
Social functioning	45.65 (44.78, 46.53)	45.62 (44.09, 47.15)	− 0.03 (− 1.79, 1.73)	45.21 (43.31, 47.12)	45.62 (44.09, 47.15)	0.41 (− 2.03, 2.85)

Weighted using the estimated propensity score; Confounders include age at diagnosis, time from diagnosis to survey, year of diagnosis, race/ethnicity, marital status, education level, stage, grade, histologic subtype, lymph node assessment, comorbid conditions, and difficulty with activities of daily living

SF-36 RAND Short-Form 36, *VR-12* Veterans RAND 12, *RT* radiation therapy

Data for means and differences in means by RT type are shown in Supporting Tables 2, 3.

Discussion

Currently, our study is the largest U.S. population-based cohort study to investigate HRQOL data associated with adjuvant RT for older women with early-stage EC. In our study,

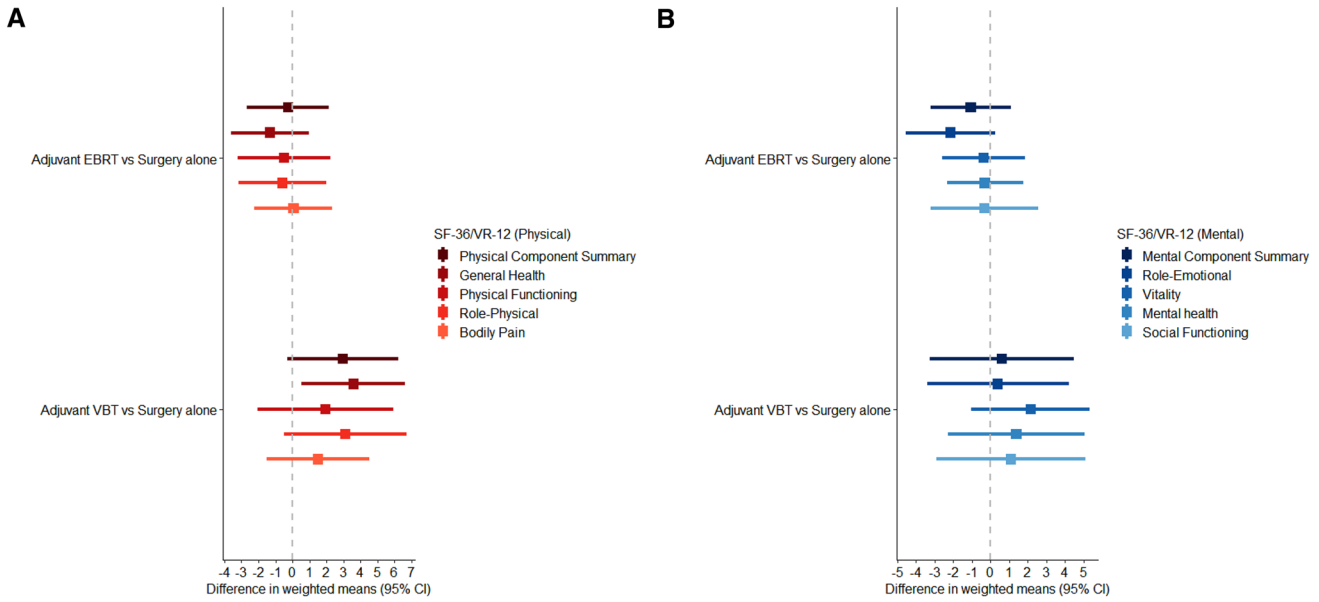

Fig. 2 Differences in weighted means with 95% CIs of SF-36/VR-12 **A** physical HRQOL *T*-scores for Adjuvant EBRT (index) vs Surgery alone (referent) and Adjuvant VBT (index) vs Surgery alone (referent), **B** mental HRQOL *T*-scores for Adjuvant EBRT (index) vs Surgery alone (referent) and Adjuvant VBT (index) vs Surgery alone (referent). Weighted using the estimated propensity score; Confounders include age at diagnosis, time from diagnosis to survey, year of diagnosis, race/ethnicity, marital status, education level, stage, grade, histologic subtype, lymph node assessment, comorbid conditions, and difficulty with activities of daily living. *EBRT* external beam radiation therapy, *VBT* vaginal brachytherapy, *RT* radiation therapy, *SF-36* RAND Short-Form 36, *VR-12* Veterans RAND 12

physical and mental HRQOL scores, measured via SF-36/VR-12 and assessed a median of 5.2 years after the cancer diagnosis, was not associated with adjuvant RT receipt. When stratified by RT type, no statistically significant associations were observed for adjuvant VBT and physical or mental health, or for adjuvant EBRT and any HRQOL domain. Women treated with adjuvant VBT reported slightly better general health subscale scores compared to women treated with surgery alone, however caution should be used interpreting these results based on statistical difference, as clinically meaningful difference should be examined further to confirm the findings.

No difference in HRQOL scores between patients treated with adjuvant RT and surgery alone in the current study was not consistent with finding from a prospective cohort study of 221 EC survivors [30]. In this study, Zandbergen et al. reported that EC patients who received RT compared to surgery showed greater improvements in emotional and cognitive functioning scales over time. However, the results may be biased due to uncontrolled confounding by underlying severity of the disease, as lost-to-follow-up due to death or ill-health was higher in RT group vs surgery group, which is likely that these differences are driven by baseline differences in clinical characteristics between the groups. Therefore, our differing results could be due to our adjustment for underlying tumor- and clinical characteristics.

The Postoperative Radiotherapy for Endometrial Cancer (PORTEC-1) trial suggests avoiding EBRT in early-stage patients with low- and intermediate risk EC due to its association with long-term urinary and bowel symptoms leading to poor HRQOL [31]. Additionally, in a multicenter cross-sectional survey of early-stage EC survivors (years from diagnosis to survey, mean = 8.0) [32], EBRT use was negatively associated with the SF-36 subscales "vitality", "social functioning", and "mental health". In contrast, our study found no association between EBRT and poor HRQOL. Although it is difficult to directly compare these results to ours, as the prior studies have focused on women of all ages rather than older women, our differing results from the prior studies may be due, in part, to our adjustment for stage, grade, and histologic subtype. Similarly, van de Poll-Franse et al. [33] reported no association after the adjustment for confounders among women with stage I–II disease.

Many women who were previously treated with EBRT are now more frequently treated with VBT as a result of its comparable locoregional control and more favorable HRQOL profile, as demonstrated by the PORTEC-2 trial [7]. However, whether adjuvant VBT is associated with better HRQOL when compared to surgery alone group remains unclear due to lack of evidence from clinical trials. Few observational studies have addressed this question, and studies have often had small sample sizes from single institutions [34, 35]. In a single center study of 69 women with

early-stage cancer, Quick et al. reported no significant differences in the overall HRQOL for women treated VBT vs. surgery alone. In addition, in another single center study of 205 women with early-stage cancer, Damast et al. reported that VBT receipt (relative to surgery alone) was associated with favorable HRQOL (5.91 points higher in general health state of the EuroQoL EQ5D visual analog scale, $p = 0.0183$). In our investigation, we confirmed that adjuvant VBT was associated with significantly better general health compared to surgery alone (3.59 points higher in physical functioning of the SF-36/VR-12, 95% CI 0.56–6.62) in a more representative U.S. population-based sample of women with early-stage cancer. Our findings indicate that VBT provides better HRQOL compared to surgery alone. However, given that current evidence has not been able to incorporate the patients' baseline pre-treatment HRQOL scores, further prospective longitudinal investigation on HRQOL score changes related to pre- to post-treatment is needed to confirm these findings. Furthermore, although our analyses adjusted for important measurable prognostic and clinical variables, the favorable outcome associated with VBT may have been affected by residual confounding by indication.

A strength of our study was the utilization of large U.S. population-based cancer data from SEER linked to survey data from MHOS. Leveraging these data resources provided an efficient, large-scale opportunity to evaluate long-term HRQOL outcomes after adjuvant RT in a group of older women treated for early-stage EC in real-world oncology practice. Another strength of the present study was the control of underlying prognostic factors (i.e., stage, grade, histologic subtype), as well as important clinical factors (i.e., ADL, comorbid conditions). The control of these key confounders allowed us to improve methodological shortcomings of prior literature and produce more robust estimates of the association between adjuvant RT and HRQOL.

Despite these strengths, limitations should be considered. Because the SEER-MHOS does not contain data on Medicare fee-for-service beneficiaries [36], our results may not be generalizable to the entire Medicare population. In addition, due to lack of administrative claims data, we were unable to quantify or control important treatment-related covariates that affect HRQOL outcome. Another limitation is that women had to be alive and healthy enough to be able to complete the survey, and therefore women who are very sick and therefore have extremely poor QOL are likely to be excluded from our analysis, which could lead to selection bias. The MHOS also lacked disease-specific patient-reported outcome measures, which contain symptom items that are more relevant to radiation-induced side effects. Therefore, disease and treatment specific aspects of the HRQOL (i.e., sexual function, bowel symptoms, vaginal symptoms, lymphedema) were not evaluated. Lastly, because the MHOS was not designed around cancer surveillance, few women in our sample completed the MHOS both before and after their treatment, and thus we were under-powered to adjust for women's pre-treatment HRQOL scores.

In summary, older women with early-stage EC treated with adjuvant RT did not report worse physical and mental HRQOL scores compared to those treated with surgery alone, though relevant symptoms should be evaluated further to fully understand the disease and treatment specific aspects of the HRQOL. VBT provided better general health compared to surgery alone in the analyses of eight subscales, however more detailed baseline clinical data are needed to consider this association carefully, as this may reflect underlying severity of the disease. Our findings provided much needed data on patient-reported outcomes that should be discussed between oncologists and patients when making treatment decisions as patient-reported HRQOL profiles may help inform optimal treatment approaches for older women with early-stage EC.

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Author contributions JP: Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing—Original Draft, Review & Editing. EEK, JLL, CA, AFO, and WRB: Methodology, Writing—Review & Editing. HBN: Conceptualization, Methodology, Writing—Review & Editing, Supervision.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest Jennifer L. Lund receives salary support to the University of North Carolina at Chapel Hill from the Center for Pharmacoepidemiology (Current Members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim) and from other pharmaceutical companies (AbbVie, Roche). Her spouse was formerly employed by GlaxoSmithKline and previously owned stock in the company. Jihye Park, Erin E. Kent, Chelsea Anderson, Andrew F. Olshan, Wendy R. Brewster, and Hazel B. Nichols have no conflict of interest to disclose.

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