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Overuse of External Beam Radiotherapy for Stage I Endometrial Cancer

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Abstract

Background—Radiation therapy has long been part of the treatment of endometrial cancer. Despite the long history of radiation use, prospective trials in the U.S. and Europe have been unable to demonstrate a survival benefit with adjuvant radiotherapy compared to observation. While radiation has been associated with decreased rate of loco-regional failure, the treatment is also associated with substantial toxicity. However, a randomized trial published in 2010 demonstrated that, compared to external beam radiation therapy (EBRT), vaginal brachytherapy was less toxic and as effective in reducing loco-regional relapses.

Objective—We examined patterns of use of external beam radiation therapy for women with high intermediate risk endometrial cancer.

Study Design—We examined the use of external beam radiation therapy in women registered in the National Cancer Data Base with high intermediate risk, stage I endometrial cancer treated from 2008–2012. High intermediate risk was defined as: age > 60 years with a stage IA, grade 3 tumors or stage IB, grade 1 or 2 tumors. Multivariable models of EBRT use were developed.

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There are no conflicts of interest or disclosures.

Results—Among 8242 women, 915 (11.1%) received external beam radiation therapy, 2614 (31.7%) were treated with brachytherapy, and 4713 (57.2%) did not receive any adjuvant radiation. The use of external beam radiation therapy was 18.1% in 2008 and declined to 8.6% in 2012, while use of brachytherapy rose each year from 26.5% in 2008 to 37.6% in 2012 ($P<0.0001$). External beam radiation was administered to 7.9% of patients with stage IA/grade 3 tumors, 8.8% of those with stage IB/grade 1 cancers and to 15.2% of women with stage IB/grade 2 neoplasms ($P<0.0001$). External beam radiation therapy was utilized in 10.1% of women who underwent lymphadenectomy compared to 22.0% who did not undergo lymphadenectomy ($P<0.0001$). In a multivariable model, black women were more likely to receive external beam radiation therapy than white women (RR=1.33; 95% CI, 1.03–1.70). Similarly, patients in the eastern U.S., those treated at community cancer centers and comprehensive community cancer programs, patients in metropolitan areas, and those diagnosed in earlier years were more likely to undergo external beam radiation therapy. Patients with stage IB/grade 2 tumors (RR=1.96; 95% CI, 1.65–2.32) were more likely to receive external beam radiation therapy than those with stage IA/grade 3 neoplasms. Those women who did not undergo lymphadenectomy were more than twice as likely to receive external beam radiation therapy compared to those who had a lymphadenectomy (RR=2.32; 95% CI, 1.99–2.72).

Conclusion—Despite data from randomized trials, approximately 9% of women with high intermediate risk endometrial cancer continue to receive external beam radiation therapy. Performance of lymphadenectomy is associated with lower likelihood of external beam radiation therapy.

Introduction

Radiation therapy has long been part of the treatment of endometrial cancer.^{1–4} Most commonly, adjuvant radiation therapy has been administered after hysterectomy. Despite the long history of radiation use, prospective trials have been unable to demonstrate a survival benefit with adjuvant radiotherapy.^{1–5} The Gynecologic Oncology Group (GOG protocol 99) and the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-1) trials compared external beam radiotherapy (EBRT) to observation in women with stage I endometrial cancer. Both trials demonstrated that EBRT reduced loco-regional recurrences but did not impact overall survival.^{1, 2} Further, EBRT was associated with substantial toxicity.^{1, 2}

Although these reports failed to demonstrate an improvement in survival with EBRT, both of these studies subsequently defined a higher risk group of patients who derived the greatest absolute benefit from EBRT in reducing loco-regional relapse. Termed high intermediate risk (HIR), this group is based on a combination of factors including advanced age, grade, depth of myometrial invasion, and lymphovascular space invasion. A follow-up investigation, PORTEC-2, which was limited to early-stage, HIR patients, compared vaginal brachytherapy to EBRT.⁶ Published in 2010, PORTEC-2 found that vaginal brachytherapy was as effective as EBRT in reducing loco-regional recurrences, and was substantially less toxic.⁶

Based on these studies, vaginal brachytherapy is the favored method of radiation delivery when adjuvant radiotherapy is administered for early stage endometrial cancer.⁶ To date, few studies have examined the trends in the use of adjuvant radiotherapy since the reporting of the PORTEC-2 trial. We performed a population-based analysis to examine the patterns of use of adjuvant radiation in women with HIR, stage I endometrial cancer.

Methods

The National Cancer Data Base (NCDB) was utilized for analysis.^{7, 8} NCDB is sponsored by the American College of Surgeons and American Cancer Society and collects data on patients from across the U.S on incident cancer cases from over 1500 Commission on Cancer affiliated hospitals. The sampling schema captures approximately 70% of all newly diagnosed cancer cases. Data on patient demographics, clinical data, tumor characteristics, staging, treatment, and overall survival is collected.^{7, 8} The Columbia University Institutional Review Board deemed the study exempt.

Women with stage I endometrioid adenocarcinomas of the endometrium treated from 2008–2012 were analyzed. The cohort was limited to women with high intermediate risk (HIR) tumors as defined by the PORTEC-2 study group: age > 60 years with a stage IA, grade 3 tumors or stage IB, grade 1 or 2 tumors.⁶ Based on the revised FIGO staging criteria, patients with <50% myometrial invasion, including those with tumors confined to the endometrium, were classified as stage IA neoplasms.⁶ Patients were stratified based on receipt of radiation into the following groups: no radiation, brachytherapy, and external beam radiation (EBRT) (either alone or in combination with brachytherapy). Receipt of radiation either at the center where a patient was diagnosed or at another facility were captured as radiation treatment.

Clinical variables analyzed included age (61–70, 71–80, >80 years), race (white, black, Hispanic, other, unknown), insurance (private, Medicare, Medicaid, uninsured, other), region of residence (eastern, south, Midwest, west), and location (metropolitan, urban, rural, and unknown). Performance of lymphadenectomy was noted for each patient. Comorbidity was measured using the Deyo classification of the Charlson comorbidity score (0, 1, 2).^{9, 10} A combination of tumor stage and grade were utilized to categorize patients as: stage IA/grade 3, stage IB/grade 1, stage IB/grade 2. Hospital location was classified as metropolitan, urban, or rural. Facility type (academic/research, comprehensive community cancer center, or community cancer center) was defined by the American Cancer Society's Commission on Cancer as: academic/research hospitals (institutions affiliated with university medical schools or those designated as National Cancer Institute Comprehensive Cancer programs), community cancer centers (institutions that diagnose or treat 100–649 cancer cases annually) and comprehensive community centers (institutions that diagnose or treat ≥ 650 cancer cases annually).^{8, 11}

Frequency distributions for categorical variables were analyzed based on receipt of external beam radiation using χ^2 tests. Multivariable generalized estimating equations (GEE) with a Poisson distribution and log link function were developed to examine predictors of EBRT while adjusting for other clinical, demographic, and hospital characteristics. Results are

reported with risk ratios and 95 confidence intervals (95% CI). Sensitivity analyses were performed after stratifying the cohort based on performance of lymphadenectomy. All analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All analyses were two-tailed and a P -value of <0.05 was considered statistically significant.

Results

We identified a total of 8242 women with high intermediate risk endometrial cancer treated from 2008–2012. Overall, 915 (11.1%) received EBRT, 2614 (31.7%) were treated with brachytherapy, and 4713 (57.2%) did not receive any adjuvant radiation. The use of external beam therapy was 18.1% in 2008, declined to 8.5% in 2010 and then rose slightly to 9.8% in 2011 and 8.6% in 2012. In contrast, utilization of brachytherapy rose each year from 26.5% in 2008 to 37.6% in 2012 ($P<0.0001$) (Figure 1).

Table 1 displays the clinical and demographic characteristics of the cohort. External beam radiation was administered to 7.9% of patients with stage IA/grade 3 tumors, 8.8% of those with stage IB/grade 1 cancers and to 15.2% of women with stage IB/grade 2 neoplasms ($P<0.0001$) (Table 1). EBRT was utilized in 10.1% of women who underwent lymphadenectomy compared to 22.0% who did not undergo lymphadenectomy ($P<0.0001$). In an univariate analysis, EBRT was more commonly used in younger women, those with some type of insurance, those with no comorbidities, women who did not undergo lymphadenectomy, patients with stage IB/grade 2 tumors, residents of the eastern US and those residing in metropolitan areas and women treated at community cancer programs. Use of vaginal brachytherapy increased substantially over time. In a multivariable model, black women were more likely to receive EBRT than white women (RR=1.33; 95% CI, 1.03–1.70). Similarly, patients in the eastern U.S., those treated at community cancer centers and comprehensive community cancer programs, patients in metropolitan areas, and those diagnosed in earlier years were more likely to undergo EBRT (Table 2). Patients with stage IB/grade 2 tumors (RR=1.96; 95% CI, 1.65–2.32) were more likely to receive EBRT than those with stage IA/grade 3 neoplasms. Those women who did not undergo lymphadenectomy were more than twice as likely to receive EBRT compared to those who had a lymphadenectomy (RR=2.32; 95% CI, 1.99–2.72).

When stratified by performance of lymphadenectomy, the factors associated with use of external beam radiation were largely unchanged among women who underwent lymph node dissection. In this model, the risk ratio for receipt of EBRT in women with stage IB/grade 2 tumors compared to stage IA/grade 3 tumors was 2.01 (95% CI, 1.67–2.41). Among those women who did not undergo lymphadenectomy, region, type of treatment center, year of diagnosis and grade and stage were associated with use of EBRT.

Discussion

These data suggest that while use of EBRT for HIR stage I endometrial cancer has decreased, nearly 10% of women with HIR tumors still receive the treatment. While clinical and demographic factors are associated with the use of EBRT, performance of lymphadenectomy strongly influences the choice to use EBRT.

Although radiation has long been a part of the treatment of endometrial cancer, use of EBRT for HIR endometrial cancer is problematic as the therapy is associated with significant toxicity and cost in the absence of clinical benefit compared to observation or brachytherapy.^{1, 2, 6, 12, 13} In the PORTEC-2 trial, grade 1 and 2 gastrointestinal toxicity was noted in 54% of women who received EBRT compared to 13% of those treated with brachytherapy, while late grade 3 gastrointestinal events occurred in 2% and <1% of the groups, respectively.⁶ These differences decreased over time while vaginal atrophy was more common with brachytherapy.⁶ In addition to toxicity, EBRT is substantially more costly than vaginal brachytherapy. Cost analyses have suggested that the cost of a course of brachytherapy (high dose rate) is approximately \$1000-\$1800 less than EBRT.^{13, 14}

Prior studies examining the adoption of evidence to guide adjuvant radiation therapy for endometrial cancer have reported mixed findings.^{15, 16} One population-based analysis found no difference in the overall use of radiotherapy after publication of both GOG 99 and PORTEC-1. The lack of change in use of radiation was noted for both intermediate and high-intermediate risk patients.¹⁵ Of note, this study found that use of EBRT decreased from 2000 to 2007 while the use of vaginal brachytherapy began to increase during the same time period.¹⁵ The increase in the use of brachytherapy in this reported occurred prior to the publication of the PORTEC-2 study findings in 2010. Although data from randomized trials was not available, several studies in the 1990's and 2000's had described the safety of brachytherapy.^{13, 17-19} In the current analysis we noted that EBRT decreased substantially from 2008 to 2012 while the use of brachytherapy increased.

We noted that women who underwent lymphadenectomy were less likely to receive EBRT. Performance of lymphadenectomy for women with apparent stage I endometrial cancer remains an area of controversy. While two randomized trials have failed to demonstrate a survival benefit with lymphadenectomy, one potential benefit of the procedure is that it can help tailor adjuvant therapy.^{20, 21} An analysis of the Surveillance, Epidemiology, and End Results database found that women with tumors invading <50% of the myometrium and women with grade 1 or 2 tumors and >50% myoinvasion were less likely to receive EBRT and more likely to be treated with vaginal brachytherapy.²² Although women enrolled in the PORTEC trials were not required to undergo lymphadenectomy, the risk of occult nodal disease in women who did not undergo lymph node evaluation was likely an important factor influencing use of EBRT in our cohort.

In addition to clinical and tumor characteristics, a number of demographic and systems factors were associated with use of EBRT. Compared to white women, black women were over 30% more likely to receive EBRT. Prior studies have shown that black women are at increased risk for death from uterine cancer, even when matched by stage, and that there are numerous disparities in the care black women receive.²³⁻²⁶ We also noted that patients treated at academic centers were less likely to receive EBRT. Data describing the influence of hospital characteristics on outcomes for uterine cancer are limited.

While our study benefits from the inclusion of a large cohort of women, we recognize a number of important limitations. First, we cannot exclude the possibility that receipt of radiation was miscoded in a small number of patients. However, NCDB has a rigorous

quality control process and captures radiation both at the center where the cancer was diagnosed, as well as any additional treatment centers a patient may have attended. Therefore, the possibility of misclassification is likely not sufficient to attenuate our findings. Second, some clinical and pathologic features that may have influenced the choice to utilize adjuvant radiation, such as lymphovascular space invasion and cytologic washings, are not captured. Lastly, as with any study using administrative data, we cannot capture individual physician and patient preferences that influenced the use of adjuvant therapy.

Despite the toxicity and increased cost of EBRT, a substantial number of women continue to receive the treatment. Overuse of EBRT is likely multifactorial and driven by both patient and physician and systems factors. These data suggest that performance of lymphadenectomy and knowledge of the nodal status reduced the use of EBRT by more than 50% potentially suggesting an important role for lymph node dissection in this population. Given these data, further efforts to define the appropriate role of EBRT for women with HIR endometrial cancer as well as to promote the use of vaginal brachytherapy in lieu of EBRT when appropriate are warranted.

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Figure 1.

Use of external beam radiation therapy and brachytherapy for stage 1 endometrial cancer. 1A. All patients. 1B. Women who underwent lymphadenectomy. 1C. Women who did not undergo lymphadenectomy. Blue line represents vaginal brachytherapy and red line external beam radiation therapy.

Table 1

Clinical and demographic characteristics associated with use of radiation therapy.

	No radiation		External beam radiotherapy		Vaginal brachytherapy		<i>P-value</i>
	N	(%)	N	(%)	N	(%)	
<i>Year of diagnosis</i>	4713	(57.2)	915	(11.1)	2614	(31.7)	<0.0001
2008	779	(55.4)	255	(18.1)	372	(26.5)	
2009	776	(58.3)	166	(12.5)	390	(29.3)	
2010	1,105	(60.9)	154	(8.5)	556	(30.6)	
2011	1,080	(57.5)	184	(9.8)	615	(32.7)	
2012	973	(53.8)	156	(8.6)	681	(37.6)	
<i>Age (years)</i>							<0.0001
61–70	2,588	(55.2)	542	(11.6)	1,559	(33.2)	
71–80	1,451	(55.8)	304	(11.7)	847	(32.6)	
>80	674	(70.9)	69	(7.3)	208	(21.9)	
<i>Race/ethnicity</i>							0.04
White	4,000	(56.7)	773	(10.9)	2,287	(32.4)	
Black	296	(57.4)	66	(12.8)	154	(29.8)	
Hispanic	204	(63.6)	39	(12.1)	78	(24.3)	
Other	140	(60.6)	23	(10.0)	68	(29.4)	
Unknown	73	(64.0)	14	(12.3)	27	(23.7)	
<i>Insurance status</i>							0.03
Private insurance	1,302	(54.8)	261	(11.0)	812	(34.2)	
Medicaid	103	(52.6)	23	(11.7)	70	(35.7)	
Medicare	3,110	(58.0)	606	(11.3)	1,645	(30.7)	
Not insured	112	(65.5)	16	(9.4)	43	(25.1)	
Other government/unknown	86	(61.4)	9	(6.4)	45	(32.1)	
<i>Comorbidity</i>							0.16
0	3,377	(56.5)	675	(11.3)	1,928	(32.2)	
1	1,067	(58.3)	196	(10.7)	566	(30.9)	

	No radiation		External beam radiotherapy		Vaginal brachytherapy		<i>P</i> -value
	N	(%)	N	(%)	N	(%)	
2	269	(62.1)	44	(10.2)	120	(27.7)	
<i>Lymph nodes examined</i>							<0.0001
Yes	4,270	(56.8)	756	(10.1)	2,493	(33.2)	
No	443	(61.3)	159	(22.0)	121	(16.7)	
<i>Stage and grade</i>							<0.0001
Stage IA/grade 3	1,313	(60.6)	172	(7.9)	680	(31.4)	
Stage IB/grade 1	1,746	(61.2)	252	(8.8)	853	(29.9)	
Stage IB/grade 2	1,654	(51.3)	491	(15.2)	1,081	(33.5)	
<i>Region</i>							<0.0001
Eastern	787	(42.8)	254	(13.8)	796	(43.3)	
South	1,460	(65.1)	188	(8.4)	596	(26.6)	
Midwest	1,618	(57.8)	353	(12.6)	829	(29.6)	
West	848	(62.3)	120	(8.8)	393	(28.9)	
<i>Location</i>							0.001
Metropolitan	3,636	(56.4)	741	(11.5)	2,073	(32.1)	
Urban	795	(59.0)	124	(9.2)	429	(31.8)	
Rural	103	(61.7)	13	(7.8)	51	(30.5)	
Unknown	179	(64.6)	37	(13.4)	61	(22.0)	
<i>Facility type^J</i>							<0.0001
Academic	1,784	(54.8)	303	(9.3)	1,171	(35.9)	
Community cancer program	221	(55.4)	90	(22.6)	88	(22.1)	
Comprehensive community cancer program	2,702	(59.1)	520	(11.4)	1,353	(29.6)	

^J Cells with <10 observations not presented.

Table 2

Multivariable models of factors associated with use of external beam radiotherapy.

		Entire cohort	Lymphadenectomy performed	No lymphadenectomy
		RR (95% CI)	RR (95% CI)	RR (95% CI)
<i>Year of diagnosis</i>				
	2008	2.16 (1.78–2.62) *	2.30 (1.85–2.86)	1.65 (1.07–2.55) *
	2009	1.49 (1.21–1.84) **	1.53 (1.21–1.94) **	1.41 (0.91–2.18)
	2010	Referent	Referent	Referent
	2011	1.20 (0.97–1.49)	1.18 (0.93–1.50)	1.51 (0.96–2.37)
	2012	1.05 (0.83–1.34)	1.02 (0.78–1.34)	1.25 (0.80–1.96)
<i>Age (years)</i>				
	61–70	Referent	Referent	Referent
	71–80	0.98 (0.85–1.13)	1.02 (0.87–1.20)	0.81 (0.59–1.12)
	>80	0.51 (0.40–0.65) **	0.52 (0.39–0.69) **	0.47 (0.31–0.74) *
<i>Race/ethnicity</i>				
	White	Referent	Referent	Referent
	Black	1.33 (1.03–1.70) *	1.48 (1.13–1.93) *	0.72 (0.37–1.41)
	Hispanic	1.15 (0.83–1.60)	1.21 (0.83–1.77)	0.91 (0.49–1.70)
	Other	1.04 (0.69–1.57)	1.15 (0.74–1.77)	0.39 (0.06–2.65)
	Unknown	1.25 (0.78–2.00)	1.10 (0.63–1.93)	1.74 (0.86–3.53)
<i>Insurance status</i>				
	Private insurance	Referent	Referent	Referent
	Medicaid	1.08 (0.74–1.57)	1.02 (0.67–1.54)	1.48 (0.61–3.55)
	Medicare	1.02 (0.87–1.20)	0.97 (0.82–1.15)	1.42 (0.99–2.04)
	Not insured	0.90 (0.59–1.36)	0.84 (0.52–1.36)	1.47 (0.54–3.96)
	Other government/unknown	0.65 (0.34–1.25)	0.62 (0.30–1.31)	0.78 (0.19–3.17)
<i>Comorbidity</i>				
	0	Referent	Referent	Referent
	1	0.92 (0.79–1.07)	0.94 (0.80–1.11)	0.84 (0.59–1.19)
	2	0.84 (0.63–1.11)	0.84 (0.60–1.16)	0.84 (0.52–1.35)
<i>Lymph nodes examined</i>				
	Yes	Referent	-	-
	No	2.32 (1.99–2.72) **	-	-
<i>Stage/grade</i>				
	Stage IA/grade 3	Referent	Referent	Referent
	Stage IB/grade 1	1.09 (0.90–1.32)	1.07 (0.86–1.33)	1.13 (0.76–1.68)
	Stage IB/grade 2	1.96 (1.65–2.32) **	2.01 (1.67–2.41) **	1.63 (1.10–2.43) *
<i>Region</i>				
	Eastern	Referent	Referent	Referent
	South	0.59 (0.47–0.75) **	0.62 (0.47–0.80) *	0.49 (0.32–0.75) *

		Entire cohort	Lymphadenectomy performed	No lymphadenectomy
		RR (95% CI)	RR (95% CI)	RR (95% CI)
<i>Location</i>	Midwest	0.92 (0.75–1.14)	0.91 (0.73–1.15)	0.97 (0.68–1.37)
	West	0.60 (0.47–0.78) **	0.59 (0.45–0.78) *	0.64 (0.40–1.03)
	Metropolitan	Referent	Referent	Referent
	Urban	0.75 (0.62–0.91) *	0.75 (0.61–0.92) *	0.73 (0.48–1.09)
	Rural	0.66 (0.38–1.15)	0.68 (0.35–1.31)	0.70 (0.30–1.62)
<i>Facility type</i>	Unknown	1.14 (0.85–1.52)	1.19 (0.86–1.63)	0.78 (0.37–1.65)
	Academic	Referent	Referent	Referent
	Community cancer program	2.22 (1.73–2.85) **	2.27 (1.71–3.01) **	1.79 (1.16–2.76) *
	Comprehensive community cancer program	1.27 (1.05–1.53) *	1.29 (1.05–1.58) *	1.18 (0.84–1.64)
	Other	1.84 (1.50–2.25) **	1.91 (1.52–2.38) **	-

Risk ratio (95% confidence interval).

*
P<0.05,

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P<0.0001