



## The role of adjuvant radiation in lymph node positive endometrial adenocarcinoma



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### HIGHLIGHTS

- A national registry is used to examine the impact of radiotherapy for lymph node positive endometrial cancer.
- In this large dataset, adjuvant radiation improved overall survival in patients with lymph node positive endometrial cancer.
- Adjuvant radiation improved cancer specific survival in patients with lymph node positive endometrial cancer.
- Aggressive local therapy may improve outcomes in patients with locally advanced endometrial cancer.

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### ABSTRACT

**Objectives.** The purpose of this study was to examine the impact of adjuvant radiation on overall survival (OS) and cancer specific survival (CSS) in patients with lymph node (LN) positive endometrial cancer.

**Methods.** We analyzed all women diagnosed with FIGO stage IIIc endometrial adenocarcinoma in the Surveillance, Epidemiology, and End Results database from 2004 to 2012 ( $n = 2177$ ). Patients not undergoing surgery or with missing treatment information were excluded. Chi-squared tests were used to compare predictors of treatment received. Cox proportional hazards model and Kaplan-Meier method were used to assess OS and CSS.

**Results.** The median age was 60 (27–84) and the median follow-up was 31 months (2–107). Adjuvant radiation was administered to 1248 (60.3%) patients. A total of 1363 (65.9%) patients had pelvic LN involvement while 658 (31.8%) had para-aortic involvement. The 3-year actuarial OS for patients with and without radiation was 80.5% and 67.6%, respectively ( $p < 0.001$ ). The 3-year actuarial CSS for patients with and without radiation was 83.4% and 73%, respectively ( $p < 0.001$ ). On multivariable analysis, receipt of radiotherapy remained associated with OS (HR 0.61 95% CI 0.51–0.74) and CSS (HR 0.65, 95% CI 0.53–0.80). After propensity matching, radiotherapy continued to be associated with an improved OS (HR 0.65 95% CI 0.54–0.78) and CSS (HR 0.65 95% CI 0.53–0.81). The addition of brachytherapy was not associated with OS or CSS.

**Conclusions.** In this large population registry analysis, adjuvant radiation was associated with improved OS and CSS in patients with LN positive endometrial cancer. Prospective data is needed to confirm these findings.

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### 1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States with an estimated 54,870 cases and 10,170 deaths in 2015 [1]. The majority of patients who ultimately die of endometrial cancer have locally advanced disease and/or adverse prognostic features such as higher grade, older age, or unfavorable histology [2]. Patients diagnosed with locally advanced disease are typically offered multimodality consisting of surgery followed by chemotherapy with

or without radiation. Although the utilization of radiation therapy has been controversial in patients with locally advanced disease, recent data has suggested that the addition of radiation to chemotherapy may improve treatment outcomes [3–5]. Current guidelines leave radiotherapy use at the discretion of the treating physicians [6].

Lymph node metastases are one of the most ominous prognostic factors in patients diagnosed with endometrial cancer. An analysis by the Gynecologic Oncology Group demonstrated a 5-year recurrence free survival of 90%, 75%, and 38% for patients with negative lymph nodes, positive pelvic lymph nodes, and positive para-aortic lymph nodes respectively [7]. The purpose of this analysis was to assess the role of post-operative radiation in patients with lymph node positive endometrial cancer undergoing curative resection in a large nationwide dataset.

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**2. Materials & methods**

**2.1. Patient selection**

The Surveillance, Epidemiology, and End Results (SEER) program is sponsored by the National Cancer Institute and collects cancer incidence, survival, and treatment information. The SEER registry covers approximately 28% of the United States population [8]. The registry includes treatment information regarding the first course of therapy such as type of surgery, lymph node evaluation, radiation use but does not include data such as chemotherapy use. Clinical information such as age, race, gender, stage, and grade is also included in the registry but there is no information on comorbidities or performance status.

The SEER registry was queried from 2004 to 2012 for patients ≥18 years old diagnosed with FIGO stage IIIC endometrial (C54.1) adenocarcinoma (8380/3) according to the American Joint Committee for Cancer Staging Version 6 staging system [9]. Only patients undergoing curative surgery (Surgical Codes 40, 50, 60–67) followed by post-operative radiation therapy were included. Patients with extranodal

metastatic disease, more than one primary, receiving neoadjuvant or IORT, or with less than one month follow-up were excluded from the analysis.

**2.2. Data analysis**

Propensity scores were constructed using a multivariable logistic regression model with receipt of radiation therapy as the treatment outcome. Covariates included in the propensity score were based on the univariate analysis and included: clinical T stage, marital status, lymph node region involved, tumor size, poverty level, and tumor grade. Propensity score matched pairs were generated using 1:1 nearest neighbor matching without replacement. Standardized differences were used to assess the success of matching; a residual imbalance <0.10 was considered a successful match. The association between demographic and clinical characteristics was compared between patients receiving radiotherapy and those who did not using Chi-squared tests in the matched and unmatched cohorts. Overall survival (OS) and cancer specific survival (CSS) for patients with or without post-operative radiation were

**Table 1**  
Patient and treatment characteristics in matched and unmatched cohort.

	Before propensity matching					After propensity matching				
	All patients		Receipt of radiation		p-value	All patients		Receipt of radiation		p-Value
	(n = 2068)	%	Yes (n = 1248)	%		(n = 1640)	%	Yes (n = 820)	%	
<b>Age</b>										
≤49 years old	265	(12.8%)	158	(59.6%)	0.269	205	(12.5%)	107	(52.2%)	0.523
50–59 years old	692	(33.5%)	421	(60.8%)		532	(32.4%)	271	(50.9%)	
60–69 years old	675	(32.6%)	424	(62.8%)		535	(32.6%)	251	(46.9%)	
70–79 years old	342	(16.5%)	194	(56.7%)		287	(17.5%)	148	(51.6%)	
>80 years old	94	(4.5%)	51	(54.3%)		81	(4.9%)	43	(53.1%)	
<b>Race</b>										
White	1680	(81.2%)	1031	(61.4%)	0.136	1321	(80.5%)	649	(49.1%)	0.355
Black	167	(8.1%)	92	(55.1%)		139	(8.5%)	75	(54.0%)	
Other/unknown	221	(10.7%)	125	(56.6%)		180	(11.0%)	96	(53.3%)	
<b>Marital status</b>										
Married	1014	(49.0%)	637	(62.8%)	0.038	743	(45.3%)	377	(50.7%)	0.614
Single/separated/divorced/widowed	996	(48.2%)	573	(57.5%)		851	(51.9%)	423	(49.7%)	
Unknown, unmarried or domestic partner	58	(2.8%)	38	(65.5%)		46	(2.8%)	20	(43.5%)	
<b>Clinical stage</b>										
T1	958	(46.3%)	582	(60.8%)	0.05	756	(46.1%)	376	(49.7%)	0.108
T2	456	(22.1%)	293	(64.3%)		355	(21.6%)	163	(45.9%)	
T3	654	(31.6%)	373	(57.0%)		529	(32.3%)	281	(53.1%)	
<b>Lymph nodes region</b>										
Pelvic	1363	(65.9%)	851	(62.4%)	0.019	1067	(65.1%)	512	(48.0%)	0.065
Para-aortic	658	(31.8%)	368	(55.9%)		543	(33.1%)	290	(53.4%)	
Not otherwise specific	47	(2.3%)	29	(61.7%)		30	(1.8%)	18	(60.0%)	
<b>Lymph nodes assessed</b>										
1–10 LN	612	(29.6%)	375	(61.3%)	0.295	476	(29.0%)	237	(49.8%)	0.462
11–20 LN	687	(33.2%)	429	(62.4%)		542	(33.0%)	258	(47.6%)	
21+	701	(33.9%)	404	(57.6%)		570	(34.8%)	297	(52.1%)	
Not otherwise specific	68	(3.3%)	40	(58.8%)		52	(3.2%)	28	(53.8%)	
<b>Tumor size</b>										
≤5 cm	807	(39.0%)	511	(63.3%)	0.06	600	(36.6%)	296	(49.3%)	0.634
>5 cm	644	(31.1%)	369	(57.3%)		532	(32.4%)	275	(51.7%)	
Unknown	617	(29.8%)	368	(59.6%)		508	(31.0%)	249	(49.0%)	
<b>% of families below poverty level</b>										
0–20th percentile	558	(27.0%)	356	(63.8%)	0.014	421	(25.7%)	202	(48.0%)	0.212
21–40th percentile	396	(19.1%)	227	(57.3%)		317	(19.3%)	169	(53.3%)	
41–60th percentile	431	(20.8%)	268	(62.2%)		350	(21.3%)	163	(46.6%)	
61–80th percentile	412	(19.9%)	224	(54.4%)		350	(21.3%)	188	(53.7%)	
81–100th percentile	271	(13.1%)	173	(63.8%)		202	(12.3%)	98	(48.5%)	
<b>% with less than high school education</b>										
0–20th percentile	520	(25.1%)	324	(62.3%)	0.195	397	(24.2%)	196	(49.4%)	0.463
21–40th percentile	458	(22.1%)	279	(60.9%)		358	(21.8%)	179	(50.0%)	
41–60th percentile	436	(21.1%)	273	(62.6%)		348	(21.2%)	163	(46.8%)	
61–80th percentile	348	(16.8%)	204	(58.6%)		284	(17.3%)	144	(50.7%)	
81–100th percentile	306	(14.8%)	168	(54.9%)		253	(15.4%)	138	(54.5%)	
<b>Grade</b>										
1	361	(17.5%)	218	(60.4%)	0.006	296	(18.0%)	143	(48.3%)	0.657
2	775	(37.5%)	493	(63.6%)		578	(35.2%)	282	(48.8%)	
3–4	607	(29.4%)	332	(54.7%)		528	(32.2%)	275	(52.1%)	
Unknown/other	325	(15.7%)	205	(63.1%)		238	(14.5%)	120	(50.4%)	

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