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Original Article

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Survival benefit of radiation in high-risk, early-stage endometrioid carcinoma

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No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Objective: To better delineate optimal management of high-risk, early-stage endometrial cancer, as national guidelines permit substantial practice variations.
Methods: Patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB grade 3 and stage II endometrioid carcinoma who underwent at least total hysterectomy were identified in SEER-Medicare. Adjuvant treatments were brachytherapy (BT), external beam radiation therapy (EBRT), and chemotherapy. Death from endometrial cancer (cancer-specific mortality [CSM]) and local recurrence were analyzed using Gray's test and Fine-Gray regression.
Results: In total, 1,095 patients were identified: 52% received BT, 56% received EBRT, 16% received chemotherapy, and 29% received no adjuvant treatment. Survival outcomes were significantly worse for stage IB grade 3 and stage II grade 3 relative to stage II grades 1–2 (5-year CSM: 18% and 23% vs. 10%; p<0.001 and p=0.003, respectively), while there was no difference between stage IB grade 3 and stage II grade 3 (p=0.618). BT had a local control benefit across all patients (p<0.001) that translated into a survival benefit in stage IB grade 3 (adjusted hazard ratio [HR] for CSM=0.47, p=0.003). EBRT had a survival benefit in stage II grade 3 (adjusted HR for CSM=0.36; p=0.031), as did lymph node dissection (p=0.015). Chemotherapy was not significantly correlated with CSM.
Conclusions: High-risk, early-stage endometrioid carcinoma is a heterogeneous population. BT was associated with a survival benefit in stage IB grade 3, whereas regional treatment with EBRT and lymphadenectomy was associated with a survival benefit in stage II grade 3.

Keywords: Endometrial Neoplasms; Brachytherapy; Radiotherapy, Adjuvant; Chemotherapy, Adjuvant; Medicare

INTRODUCTION

Approximately two-thirds of patients with endometrial carcinoma present with localized (stage I–II) disease, which comprises a wide spectrum of risk [1,2]. Women with deeply-invasive (International Federation of Gynecology and Obstetrics [FIGO] 2009 stage IB) grade 3 or stage II (cervical stromal invasion) cancer are typically considered to have the highest-risk early-stage disease.

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The optimal adjuvant management these patients is not well defined, as they were excluded from historical trials comparing adjuvant external beam radiation therapy (EBRT) versus observation (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC]-1) and EBRT versus vaginal brachytherapy (BT) (PORTEC-2) [3,4]. While stage IB grade 3 and occult stage II were eligible for Gynecological Oncology Group (GOG)-99, which compared EBRT versus observation, they comprised a small minority of the study population [2]. Additionally, the PORTEC trials and GOG-99 did not find a survival benefit with adjuvant radiation despite improved locoregional control, but they were not powered for that endpoint, and the majority of patients were of lower risk. Recently, results of the GOG-249 trial of women with higher-risk stage I or stage II disease demonstrated similar relapse-free and overall survival for BT plus chemotherapy versus pelvic EBRT [5]. However, patients with high-risk, early-stage disease may constitute a heterogeneous population, with differing levels of risk and responsiveness to therapy.

Due to these uncertainties, it is unclear who may benefit most from BT, EBRT, or both. Consensus guidelines from the National Comprehensive Cancer Network (NCCN) permit substantial variability in treatment, while the 2014 American Society for Radiation Oncology (ASTRO) guidelines recommend EBRT alone for all stage II and higher-risk stage I patients [6,7], indicating the need for further research. Therefore, we analyzed national patterns of care and cancer-specific outcomes of women with stage IB grade 3 or stage II endometrioid carcinoma. The Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used given its unique availability of data for chemotherapy, radiation, comorbidity, and cause of death. We focused on cancer-specific outcomes because it is less prone to selection bias than overall survival [8,9].

MATERIALS AND METHODS

1. Data source

The SEER registry captures all incident cancers from 17 regional registries spanning 30% of the United States population. The SEER-Medicare database links SEER cases with Medicare claims, which allows identification of patients' diagnoses and procedures across time using International Classification of Diseases (ICD) and Healthcare Common Procedure Coding System (HCPCS) codes [8,10]. All data were de-identified. The study was approved by the Stanford Institutional Review Board.

2. Cohort identification (inclusion/exclusion criteria)

We queried the 2016 release of the SEER-Medicare database for endometrial cancers diagnosed since 2004 (when modern staging information became available in SEER) with pure endometrioid adenocarcinoma (ICD-O-3 histology codes 8380–8383). Patients' stages were converted to the 2009 FIGO staging system based upon SEER variables specifying depth of myometrial invasion and cervical stromal invasion, from which stage IB grade 3 and stage II grades 1–3 patients were selected. Patients who were stage IIIA solely for positive peritoneal cytology under the previous FIGO staging system were excluded, as their 2009 FIGO stage could not be determined.

All patients underwent at least total hysterectomy according to the SEER registry. Cases in which radiation therapy was recorded as occurring preoperatively were excluded. To ensure adequate capture of Medicare claims and to analyze a more uniform population, patients

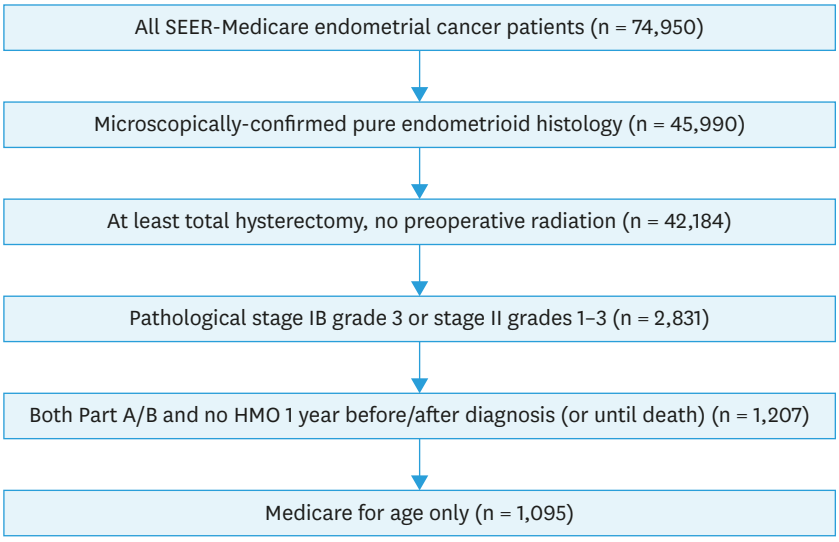

Fig. 1. Cohort identification algorithm.
HMO, health maintenance organization; SEER, Surveillance, Epidemiology, and End Results.

were required to have Medicare Parts A and B and no health maintenance organization within 12 months of diagnosis, and be enrolled in Medicare for age only [8]. **Fig. 1** summarizes the schema used to determine the study population.

3. Determination of study variables and outcomes

Variables obtained directly from the SEER registry were age, race, diagnosis year, geographical region, census tract poverty level, marital status, stage, grade, and lymph node dissection (determined as at least 1 lymph node examined by the pathologist). The extent of medical comorbidity was calculated using the Charlson comorbidity index, as described previously [8,10]. The administration of adjuvant EBRT, BT, and chemotherapy was identified using a combination of the SEER registry treatment fields and patients' Medicare claims within 9 months after diagnosis, as described previously [8].

The primary study outcome was death attributable to endometrial cancer (i.e., cancer-specific mortality [CSM]). This outcome was chosen to help offset the selection bias of more intensive therapy being administered to healthier patients, who would have increased overall survival regardless of the efficacy of the therapy [8,9]. Local recurrence was determined by the presence of diagnosis codes specifying neoplasm in the vagina, BT claims occurring more than 9 months after diagnosis, and/or claims indicating extirpative vaginal surgery (**Supplementary Table 1**). Regional nodal and distant recurrences were not assessed due to low sensitivity for capturing these outcomes by diagnosis codes [11,12]. For the 2016 SEER-Medicare linkage, patient follow-up was through December 2014.

4. Statistical analysis

Baseline characteristics were compared using Kruskal-Wallis test and χ^2 test. The cumulative incidence of endometrial CSM was estimated in the presence of other-cause mortality as a competing event. A competing risks analysis is necessary to avoid bias due to the elevated risk of non-cancer death in an elderly population [13]. For univariable analyses, CSM was compared using Gray's test [8,10]. For multivariable analyses, the proportional hazards model of Fine and Gray was used to estimate adjusted hazard ratios (HRs) for CSM. Local

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recurrence was analyzed with death as a competing event; we focused on the comparative risk (rather than the absolute risk) due to potential under-ascertainment from claims-based measures. MATLAB version R2018b (MathWorks, Inc., Natick, MA, USA) and R version 3.3.3 (R Foundation for Statistical Computing; Vienna, Austria) were used for calculations. All p-values were 2-sided and considered significant if less than 0.05.

RESULTS

A total of 1,095 patients with stage IB grade 3 (n=491) or stage II grades 1–3 (n=604) endometrioid carcinoma were identified (**Fig. 1**), whose characteristics are listed in **Table 1**. Overall, the median age was 75, 89% were white, and 76% had undergone lymph node dissection, with a median of 9 nodes removed. With respect to adjuvant therapy, 56% received EBRT and 52% received BT; 41% of all patients received both EBRT and BT, indicating that the majority of patients who received adjuvant radiation had both EBRT and BT. Additionally, 16% received chemotherapy, and 29% received no adjuvant treatment. Median follow-up was 4.8 years in living patients.

The overall 5-year risk of death due to endometrial cancer (CSM) was 15%. However, the risk was significantly higher, by approximately 2-fold, for patients with stage IB grade 3 or stage II

Table 1. Characteristics of the patients included in the study

Characteristics	All patients (n=1,095)	Stage IB grade 3 (n=491)	Stage II grades 1–2 (n=455)	Stage II grade 3 (n=149)	p-value
Age (yr)	75 (70–80)	75 (70–81)	74 (70–80)	76 (70–80)	0.531
Race					<0.001*
White	978 (89)	443 (90)	419 (92)	116 (78)	
Non-white	117 (11)	48 (10)	36 (8)	33 (22)	
Region					0.868
Northeast	337 (31)	152 (31)	139 (31)	46 (31)	
West and Midwest	238 (22)	110 (22)	98 (21)	30 (20)	
South	520 (47)	229 (47)	218 (48)	73 (49)	
Median diagnosis year	2008	2009	2008	2008	0.768
Charlson comorbidity score					0.184
0	614 (56)	285 (58)	259 (57)	70 (47)	
1	199 (18)	83 (17)	84 (18)	32 (21)	
≥2	282 (26)	123 (25)	112 (25)	47 (32)	
Marital status					0.616
Married	469 (43)	205 (42)	195 (43)	69 (46)	
Other	626 (57)	286 (58)	260 (57)	80 (54)	
Census tract poverty					0.503
<10%	607 (55)	275 (56)	256 (56)	76 (51)	
>10%	488 (45)	216 (44)	199 (44)	73 (49)	
Lymph node dissection					0.013*
No	265 (24)	99 (20)	129 (28)	37 (25)	
Yes	830 (76)	392 (80)	326 (72)	112 (75)	
Adjuvant EBRT					0.149
No	486 (44)	229 (47)	201 (44)	56 (38)	
Yes	609 (56)	262 (53)	254 (56)	93 (62)	
Adjuvant BT					<0.001*
No	524 (48)	266 (54)	190 (42)	68 (46)	
Yes	571 (52)	225 (46)	265 (58)	81 (54)	
Adjuvant chemotherapy					<0.001*
No	921 (84)	407 (83)	402 (88)	112 (75)	
Yes	174 (16)	84 (17)	53 (12)	37 (25)	

Values are presented as median (interquartile range) or number of patients (%).
BT, brachytherapy; EBRT, external beam radiation therapy.
*The p-values less than 0.05.

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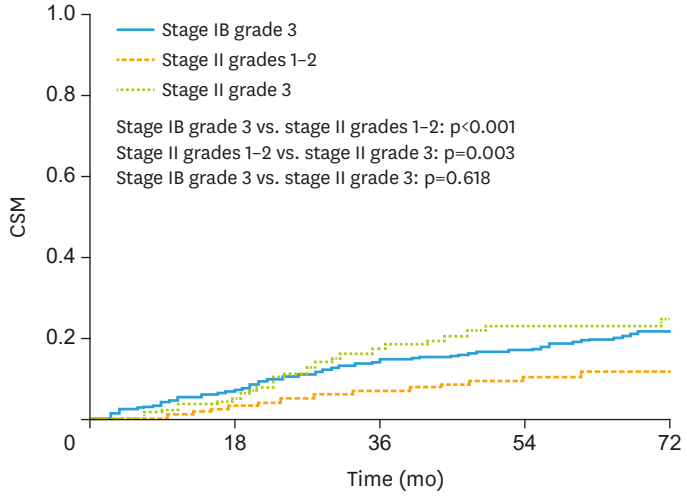

No. at risk					
Stage IB grade 3	531	455	314	217	138
Stage II grades 1–2	455	391	298	217	152
Stage II grade 3	149	123	77	56	38

Fig. 2. Endometrial CSM in patients with stage IB grade 3, stage II grades 1–2, or stage II grade 3 disease.
CSM, cancer-specific mortality.

grade 3 disease relative to stage II grades 1–2 (5-year CSM 18% and 23% vs. 10%; p<0.001 and p=0.003, respectively; **Fig. 2**). By contrast, there was no significant difference between stage IB grade 3 and stage II grade 3 patients (p=0.618; **Fig. 2**).

Due to this heterogeneity in outcomes, further analyses were performed separately in the stage IB grade 3, stage II grades 1–2, and stage II grade 3 disease cohorts. BT was used more in stage II patients than in stage IB grade 3 (54%–58% vs. 46%, p<0.001; **Table 1**). Chemotherapy was used more in stage II grade 3 than in stage IB grade 3 or stage II grades 1–2 (25% vs. 17% and 12%, p<0.001; **Table 1**). There were no significant differences in rates of EBRT (p=0.149).

BT was associated with a significant local control benefit across all patients (adjusted HR for local recurrence=0.26; 95% confidence interval [CI]=0.14–0.50; p<0.001) and within each of the disease cohorts. BT was also associated with a survival benefit across all patients (adjusted HR for CSM=0.67; 95% CI=0.48–0.94; p=0.021; **Table 2**), but when analyzed by disease cohort, the survival benefit of BT was observed specifically in stage IB grade 3 patients (5-year CSM with BT vs. without BT, 12% vs. 22%; adjusted HR for CSM=0.47; 95% CI=0.29–0.77; p=0.003; **Fig. 3**), and not in stage II grades 1–2 or stage II grade 3 patients (**Table 2**). Most (73%) of the stage IB grade 3 patients who received BT also received EBRT, while few (17%) received chemotherapy.

Compared to no adjuvant radiation, receiving BT alone was associated with a significant survival benefit in stage IB grade 3 patients (adjusted HR for CSM=0.22; 95% CI=0.06–0.77; p=0.018), but not in stage II grades 1–2 (p=0.800) or stage II grade 3 (p=0.258). Among patients who received EBRT, BT boost was administered to 63% of stage IB grade 3, 83% of stage II grades 1–2, and 74% of stage II grade 3 patients (p<0.001). Compared to EBRT alone, receiving BT in addition to EBRT was associated with a survival benefit approaching

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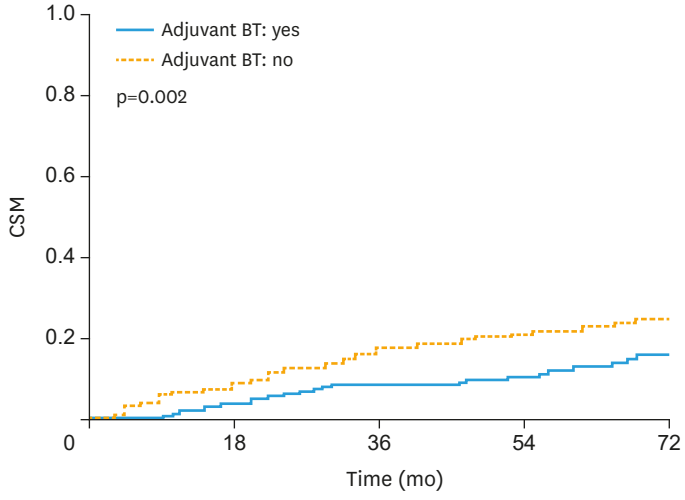
Table 2. Fine-Gray multivariable modeling of predictors for endometrial cancer-specific mortality

Variables	All patients		Stage IB grade 3		Stage II grades 1–2		Stage II grade 3	
	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Age (per year)	1.02 (0.99–1.04)	0.161	1.01 (0.97–1.04)	0.768	1.03 (0.99–1.08)	0.175	0.99 (0.93–1.06)	0.852
Race								
White	1	-	1	-	1	-	1	-
Non-white	1.51 (0.98–2.33)	0.060	1.61 (0.88–2.96)	0.125	1.51 (0.53–4.31)	0.443	1.35 (0.51–3.61)	0.549
Region								
Northeast	1	-	1	-	1	-	1	-
West	0.97 (0.55–1.72)	0.921	1.04 (0.50–2.18)	0.915	0.95 (0.30–2.99)	0.930	0.67 (0.09–4.81)	0.686
Midwest	0.89 (0.54–1.46)	0.650	0.70 (0.36–1.38)	0.306	0.80 (0.24–2.63)	0.712	1.02 (0.32–3.30)	0.971
South	0.99 (0.67–1.46)	0.955	0.75 (0.44–1.27)	0.286	1.61 (0.79–3.28)	0.192	1.07 (0.41–2.78)	0.895
Diagnosis year (per year)	0.98 (0.92–1.04)	0.468	0.94 (0.86–1.03)	0.203	0.98 (0.88–1.08)	0.672	1.12 (0.97–1.29)	0.124
Charlson comorbidity score								
0	1	-	1	-	1	-	1	-
1	1.11 (0.72–1.72)	0.635	1.06 (0.55–2.07)	0.854	0.97 (0.43–2.22)	0.947	1.87 (0.64–5.44)	0.250
≥2	1.50 (1.07–2.11)	0.019*	1.48 (0.90–2.44)	0.119	1.48 (0.76–2.91)	0.252	1.76 (0.65–4.76)	0.265
Marital status								
Married	1	-	1	-	1	-	1	-
Other	1.33 (0.96–1.85)	0.084	1.16 (0.75–1.78)	0.501	2.15 (1.09–4.25)	0.028*	1.08 (0.40–2.94)	0.874
Census tract poverty								
<10%	1	-	1	-	1	-	1	-
>10%	1.04 (0.75–1.44)	0.806	1.03 (0.65–1.64)	0.902	0.93 (0.50–1.74)	0.819	1.14 (0.50–2.58)	0.761
Lymph node dissection								
No	1	-	1	-	1	-	1	-
Yes	0.95 (0.67–1.36)	0.791	1.33 (0.72–2.45)	0.369	0.83 (0.44–1.57)	0.566	0.40 (0.19–0.84)	0.015*
Adjuvant EBRT								
No	1	-	1	-	1	-	1	-
Yes	1.08 (0.78–1.50)	0.643	1.01 (0.66–1.54)	0.983	1.37 (0.63–2.95)	0.427	0.36 (0.15–0.91)	0.031*
Adjuvant BT								
No	1	-	1	-	1	-	1	-
Yes	0.67 (0.48–0.94)	0.021*	0.47 (0.29–0.77)	0.003*	1.09 (0.53–2.23)	0.816	1.46 (0.61–3.50)	0.399
Adjuvant chemotherapy								
No	1	-	1	-	1	-	1	-
Yes	0.99 (0.63–1.57)	0.980	0.74 (0.38–1.44)	0.373	1.87 (0.80–4.33)	0.147	0.87 (0.30–2.56)	0.806

BT, brachytherapy; CI, confidence interval; EBRT, external beam radiation therapy; HR, hazard ratio.
*The p-values less than 0.05.



No. at risk					
Yes	225	197	136	103	66
No	266	216	160	102	64

Fig. 3. Endometrial CSM in patients with stage IB grade 3 disease according to status of adjuvant BT.
BT, brachytherapy; CSM, cancer-specific mortality.

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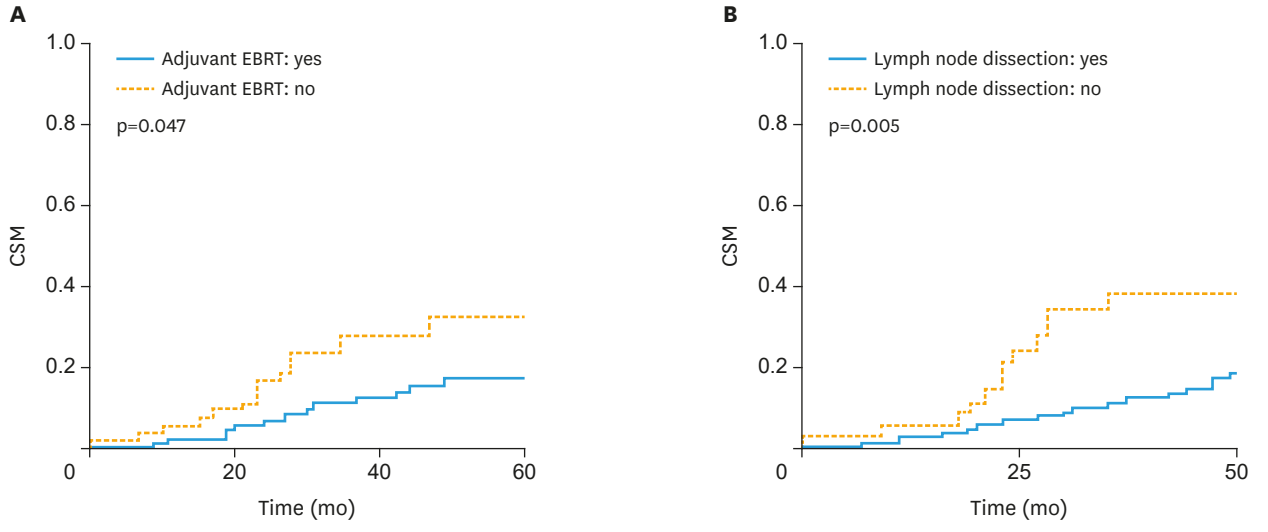

No. at risk				
Yes	93	73	48	37
No	56	45	25	11

No. at risk			
Yes	112	84	50
No	37	23	11

Fig. 4. Endometrial CSM in patients with stage II grade 3 disease according to status of (A) adjuvant EBRT and (B) lymph node dissection.
CSM, cancer-specific mortality; EBRT, external beam radiation therapy.

significance in stage IB grade 3 patients (adjusted HR for CSM=0.59; 95% CI=0.32–1.10; p=0.096), but not in stage II grades 1–2 (p=0.932) or stage II grade 3 (p=0.366).

EBRT was associated with a significant survival benefit specifically in stage II grade 3 patients (5-year CSM with EBRT vs. without EBRT, 17% vs. 33%; adjusted HR for CSM=0.36; 95% CI=0.15–0.91; p=0.031; **Fig. 4A**), and not in stage IB grade 3 (**Supplementary Fig. 1**) or stage II grades 1–2 patients (**Table 2**). Interestingly, the same pattern was observed for lymph node dissection, which significantly benefited stage II grade 3 patients (adjusted HR=0.40; 95% CI=0.19–0.84; p=0.015; **Fig. 4B**) and not the other disease cohorts (**Table 2**). Chemotherapy was not significant for CSM across all patients or in any of the disease cohorts (**Table 2**).

Table 2 lists predictors for endometrial CSM in the multivariable-adjusted analysis across all patients and within each disease cohort. Across all patients, comorbidity score was associated with increased CSM, non-white race approached significance (p=0.060), and lymph node dissection was not significant. The significant associations for EBRT and lymph node dissection in stage II grade 3 patients were only apparent in subgroup analysis within that cohort.

A sensitivity analysis was performed in which the variable for lymph node dissection was categorized as 10 or more lymph nodes removed, 1–9 lymph nodes removed, or none, which led to the same qualitative findings as before. We also performed subgroup analyses according to status of lymphadenectomy, which resulted in the same qualitative findings regarding the effect of EBRT, and an interaction term introduced for EBRT and lymph node dissection was not significant overall (p=0.777) or in any of the cohorts (p= 0.153 to p=0.633). Similarly, a sensitivity analysis of patients age 70 or younger yielded the same qualitative findings.

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DISCUSSION

High-risk, early-stage endometrioid carcinoma represented a heterogeneous population. Patients with stage IB grade 3 or stage II grade 3 disease had significantly worse survival than patients with stage II grades 1–2 disease. Furthermore, the benefit of therapy varied among these cohorts, suggesting that treatment should be individualized. BT conferred an overall local control benefit, which was expected as all patients had (by definition) deep myometrial invasion and/or cervical stromal invasion, both risk factors for vaginal cuff recurrence. Interestingly, this translated into a survival advantage specifically in stage IB grade 3 patients. On the other hand, EBRT and lymph node dissection were associated with a survival benefit specifically in stage II grade 3 patients. Chemotherapy did not confer a survival advantage in any of the analyses. Interestingly, nearly one-third of the study population received no adjuvant treatment, despite their high-risk disease.

In stage IB grade 3 patients, receipt of adjuvant BT was associated with improvements to both local control and cancer-specific mortality compared to no BT. The addition of BT to EBRT was also associated with a trend toward improved cancer-specific mortality compared to EBRT alone, although this did not reach statistical significance, likely because the effect size is smaller in the setting of already receiving EBRT. It is also possible that our results were limited by statistical power, since a relatively small minority of patients received EBRT alone. In addition, BT boost to EBRT may be more likely administered to patients with positive surgical margin. Since margin status is not available in the SEER-Medicare database, and positive margin portends a worse prognosis, this may confound (diminish) the observed benefit associated with BT boost.

Improved local control from adjuvant radiation translating into improved disease-specific survival has been shown in other cancers, such as early-stage breast cancer [14]. Vaginal relapse of grade 3 disease may place patients at high risk for synchronous or metachronous regional or distant failure, which have poor outcomes. Thus, our results suggest that deeply-invasive grade 3 patients may be best served with at least BT (with or without EBRT). BT alone has not been studied prospectively for stage IB grade 3 patients, but prospective data for EBRT in this population exist from GOG-99, suggesting that these patients should also receive at least EBRT. Taken together, these results suggest that combination EBRT plus BT may be the most preferred adjuvant approach for stage IB grade 3 patients. In comparison, the NCCN permits BT and/or EBRT, while the ASTRO guidelines recommend EBRT alone [6,7].

In the observational cohort of deeply-invasive grade 3 patients treated with pelvic EBRT alone from PORTEC-1, nearly half of first locoregional relapses were vaginal [15], suggesting local control might be increased by BT boost. Additionally, patients in the PORTEC trials did not undergo lymphadenectomy. In GOG-99, which mandated lymphadenectomy, 75% of locoregional recurrences were vaginal, and the benefit of EBRT was mostly from reduced vaginal relapse [2]. Notably, most patients in our study (including 80% of stage IB grade 3) underwent lymph node dissection, which may limit the benefit gained from EBRT, and a prior database study found that BT alone was inferior to EBRT in high-risk stage I patients if lymphadenectomy was omitted [16].

We did not find a survival benefit to EBRT in stage I grade 3 patients, which is similar to prior studies. For example, a pooled analysis of the ASTEC/EN.5 trials, which enrolled stage I patients with deep myoinvasion, grade 3, or serous/clear cell histology, found no disease-

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specific or overall survival advantage in the arm allocated to receive EBRT versus observation [17]. The EBRT arm had a modest reduction in 5-year locoregional relapse (3.2% vs. 6.1%), but less than one-third of patients underwent lymphadenectomy. Moreover, over half of participants received BT in a non-randomized fashion at the discretion of the treating physician, suggesting that outcomes were already favorable for many patients with BT alone. A recent meta-analysis of 7 trials failed to detect a cancer-specific or overall survival benefit for adjuvant EBRT in stage I patients compared to observation or BT alone, which was upheld in the subgroup of deeply-invasive grade 3 patients [18].

For stage II patients, we found that BT improved local control, but not survival. In stage II grades 1–2 patients, isolated local failure is likely more common than accompanying regional or distant failure, allowing salvage without a survival decrement. Biologically, such patients may behave similar to intermediate-risk stage I patients in PORTEC-1 and GOG-99, in whom improved local control with radiation did not translate into a survival benefit. However, the local control benefit of BT may still be desirable as salvage treatment for vaginal relapse can cause increased morbidity. Our results are consistent with prior retrospective studies suggesting that BT alone may be sufficient for most stage II patients if they underwent lymphadenectomy [19-23]. In comparison, the NCCN permits BT and/or EBRT for stage II grades 1–2 patients [7], and ASTRO guidelines recommend EBRT alone for all stage II patients [6].

Importantly, the cited studies generally did not distinguish stage II grade 3 as a separate entity, and they were only a minority (10%–25%) of the included patients. In our study, survival for stage II grade 3 patients was significantly worse compared to lower-grade stage II disease, consistent with a prior report of grade 3 as an adverse prognostic factor in stage II endometrial cancer [24]. In contrast to other stage II, we found that both EBRT and lymph node dissection conferred a survival benefit in stage II grade 3 patients, implying that they are at substantially higher risk of regional nodal metastasis and that regional (not local) control drives the disease course. Similarly, we did not find a survival advantage to BT boost in stage II grade 3 patients receiving EBRT, a local control benefit notwithstanding. In fact, such patients may be biologically more similar to stage III endometrial cancer, in which the role of adjuvant EBRT is more firmly established [6,25,26]. Notably, the NCCN recommends EBRT (with or without BT) for stage II grade 3 disease, in accordance with our findings [7].

Recent results were reported from the landmark GOG-249 trial, which randomized patients with higher-risk stage I endometrioid (as per GOG-99 high-intermediate risk criteria), stage II endometrioid, or stage I-II serous/clear cell cancer to BT with chemotherapy versus pelvic EBRT [5]. Lymphadenectomy was not required (performed in 89% of patients), and BT boost in the EBRT arm was permitted in stage II patients (and any with serous/clear cell histology). Over 80% of patients in the EBRT arm who were permitted BT boost received BT. There was no difference in local failure, distant failure, relapse-free survival, or overall survival between the treatment arms, while the EBRT arm had less regional failure and acute toxicity, implying that EBRT should be standard of care [5].

While these results offer important high-quality data, GOG-249 did not separately report survival outcomes or patterns of failure for stage IB grade 3 or stage II grade 3 patients, who have the highest levels of risk. For instance, it would be interesting to see if the regional failures in the BT/chemotherapy arm were enriched with stage II grade 3 patients, in whom we found a significant benefit for EBRT. GOG-249 may also not be sufficiently powered for these subgroup analyses; for example, the total number of stage II patients (all grades)

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was 148, which is comparable to the number of stage II grade 3 patients in this study. As we showed, high-risk early-stage endometrial cancer is a heterogeneous population with respect to level of risk and the benefit of adjuvant therapies, which may not be apparent in a combined analysis. Additionally, the added benefit of BT to EBRT cannot be assessed, since GOG-249 did not permit BT boost to stage I endometrioid patients, and the majority of stage II patients received BT boost in a non-randomized fashion. Consequently, GOG-249 leaves some important questions unresolved. Our findings suggest that high-risk early-stage patients warrant customized treatment with more granularity than can be obtained from the results of GOG-249.

Strengths of our study include its basis in national, real-world patterns of care and outcomes, and the primary endpoint of cancer-specific mortality, which is less prone to bias than overall survival [8-10]. The Medicare claims also allowed us to infer local recurrence from diagnosis codes and/or procedures associated with vaginal relapse, which was made possible by the specific proclivity for endometrial cancer to recur at the vaginal vault. Inferring local recurrence from claims-based measures may result in global under-ascertainment of the absolute recurrence rate (for example, some patients with relapse may not undergo salvage treatment). Therefore, we focused analyses on the relative risks of local recurrence, rather than the absolute rate. Regional nodal and distant recurrence were not assessed due to low sensitivity for capturing these outcomes using claims-based measures [11,12].

The main limitation of this study is its retrospective nature: residual confounding is possible, and our results should be considered hypothesis-generating. It is not possible in SEER-Medicare to distinguish sentinel lymph node biopsy from small-volume lymph node dissection; however, our results remained consistent on sensitivity analysis with lymphadenectomy categorized as 10 or more nodes removed, 1–9 removed, or none. Depth of myometrial invasion was not available for stage II patients, and lymphovascular space invasion status and surgical margin status were not available for any patient, which may influence clinical decision-making. Finally, our study comprised a Medicare-aged population (i.e., over age 65) and may not directly apply to younger patients. However, the majority of patients included in this study would be considered high-risk, regardless of age, and younger women may derive even greater survival benefit from adjuvant therapies due to fewer competing risks for death.

In summary, our results suggest that BT (with or without EBRT) may confer a cancer-specific survival benefit in stage IB grade 3 patients. BT may also be considered in stage II patients for its local control benefit. Regional treatment with EBRT and lymph node dissection were critically important in high-grade stage II disease. Additionally, grade 3 endometrioid carcinoma was itself recently shown to be heterogeneous, with several molecular subtypes with differing prognosis (POLE mutated, p53 abnormal, and mismatch repair-deficient) [27]. Given the heterogeneity of patients with high-risk early-stage disease, additional research (ideally in a prospective setting) may be needed to help address continued uncertainties and to ensure the most effective, individualized treatment is delivered.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

ICD and HCPCS codes used to identify local recurrence

Click here to view

Supplementary Fig. 1

Endometrial CSM in patients with stage IB grade 3 disease according to status of adjuvant EBRT.

Click here to view

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