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The impact of adjuvant therapy on survival in patients with FIGO Stage IB Grade 3 endometrial cancer

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Summary

Purpose of Investigation: To examine the patterns of care, predictors, and impact of adjuvant therapy on survival in patients with Stage IB Grade 3 endometrial cancer. *Materials and Methods:* The Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used to identify women 65 years or older diagnosed with Stage IB Grade 3 endometrial cancer from 1991 through 2007. *Results:* A total of 624 women were included. Adjuvant external beam radiation therapy (EBRT) was administered in 54% of the patients, while 22% received vaginal brachytherapy (VBT), and 7% received chemotherapy. In Cox-proportional hazards regression models, neither EBRT (HR: 0.94; 95% CI; 0.71–1.22), nor VBT (HR: 0.84; 95% CI: 0.60–1.17), or chemotherapy (HR: 1.30: 95% CI; 0.64–2.66) was associated with reduced mortality in patients with Stage IB Grade 3 endometrial cancer. *Conclusion:* Although commonly used; neither adjuvant radiation nor chemotherapy significantly improves survival in patients with Stage IB Grade 3 endometrial cancer.

Key words: Endometrial cancer; Adjuvant therapy; Survival.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States. It is estimated that there will be approximately 55,000 new cases and 10,000 deaths due to endometrial cancer in 2015 [1]. Most cases of endometrial cancer are diagnosed when the disease is still confined to the uterus, and have an excellent prognosis. Several adverse prognostic factors have been identified such as non-endometrioid histology, high tumor grade, deep myometrial invasion, cervical stromal invasion, and lympho-vascular space invasion [2-4]. Multiple studies have reported the potential use of these risk-factors to predict the site of recurrence [5, 6]. The subgroup of patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IB Grade 3 endometrial cancer have been reported to have a higher risk of both loco-regional and distant relapse [7, 8]. The National Comprehensive Cancer Network (NCCN) recommendation for adjuvant therapy in this situation includes a variety of options such as observation, radiation therapy [vaginal brachytherapy (VBT), external beam radiation therapy (EBRT), or both], chemotherapy, and even combined treatment with radiation and chemotherapy [9].

Endometrial cancer most commonly occurs in elderly postmenopausal women [10]. Often these patients have medical co-morbidities and poor performance status, placing them at high-risk for treatment-related toxicity [11]. Furthermore, although post-operative adjuvant treatment is directed by the predicted site of recurrence, the overall survival benefit of this approach has not been confirmed in early stage endometrial cancer [12-16]. However, patients with FIGO Stage IB Grade 3 endometrial cancer represent a unique sub-group with a distinct risk-profile. The impact of different adjuvant treatment modalities on survival in this patient population is not known as these patients were either not included or under-represented in the majority of early-stage endometrial cancer clinical trials [13, 17]. The objective of this study was to determine the practice patterns related to the administration of adjuvant therapy inpatients with FIGO Stage IB Grade 3 endometrial cancer. Additionally, the authors sought to determine the impact of adjuvant therapy on survival in this patient population. To accomplish these goals, they used a large cohort derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database of the National Cancer Institute.

Materials and Methods

Study cohort: SEER is a population-based cancer registry that collects information about patient demographics, tumor charac-

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teristics, first course of treatment, and survival for persons newly diagnosed with cancer. For people who are Medicare eligible, the Medicare database includes claims for covered healthcare services, including hospital, physician, and outpatient bills [18]. The linkage of persons in the SEER data to their Medicare claims is performed by the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services (CMS).

The eligible patients for this study were diagnosed at the age of 65 years and older with primary uterine cancer between January 1, 1991 and December 31, 2007. Only patients diagnosed with FIGO Stage IB Grade 3 endometrial cancer who underwent a cancer-directed surgery (hysterectomy) were included in the analysis. The authors excluded patients who were members of a Health Maintenance Organization at any point in the 12-month period before and after their cancer diagnosis, those enrolled in Medicare because of end-stage renal disease and dialysis, and patients with other primary tumors. This study was exempted from review by the Institutional Review Board of Wayne State University School of Medicine.

Data extraction: Age at diagnosis was classified into five-year intervals. Stage was assigned from the recorded extent-of-disease codes according to the revised 2009 FIGO staging criteria for endometrial cancer. Surgical procedure data were derived from site-specific surgery codes. Data concerning the performance of lymph node dissection and lymph node metastasis were derived from pathology codes. Information on use of adjuvant EBRT and VBT was collected. Medicare claims files [physician (NCH), outpatient (OUTPAT), and hospital (MEDPAR)] were used to identify receipt of chemotherapy within six months of cancer diagnosis. Socioeconomic status and education level of each patient was evaluated respectively by describing the median annual household income and the percentage of population with high-school education within the census tract in which the patient resided at the time of diagnosis. The study cohort was divided into approximate tertiles individually according to the median annual household income and the education level for purposes of analysis. The authors included a modified version of the Charlson co-morbidity index, which was based on the ICD-9 diagnostic and procedure codes as well as on the Healthcare Common Procedure Coding System (HCPS) codes for ten conditions, captured in the 12-month period before cancer diagnosis [19, 20]. Comorbidity index was categorized into none, one, and two or more. Area of residence was categorized as urban or rural, and the registry in which each patient was recorded was noted. Each patient's vital status at last follow-up and cause of death was recorded.

Statistical analyses: The trends of adjuvant therapy usage over time were examined using chi-square tests. Multivariable logistic regression models were developed to examine the predictors of lymphadenectomy, chemotherapy, EBRT, and VBT. The Kaplan-Meier method was used to compute survival probability data, and the log-rank test was used to compare differences between groups. Cox proportional hazards regression models were developed to examine overall survival and cancer-specific survival while controlling for other clinical and demographic characteristics. SPSS Statistics version 19 was used for all statistical analyses. All *p*-values reported are two-tailed, and a *p*-value of less than 0.05 was considered to be statistically significant.

Results

Patients: A total of 624 women met the eligibility criteria (Table 1). The mean age of the patients was 76 (range: 66–96 years) years. The majority of the patients were white and resided in urban areas. Endometrioid adenocarcinoma represented the dominant histologic sub-type (55.1%).

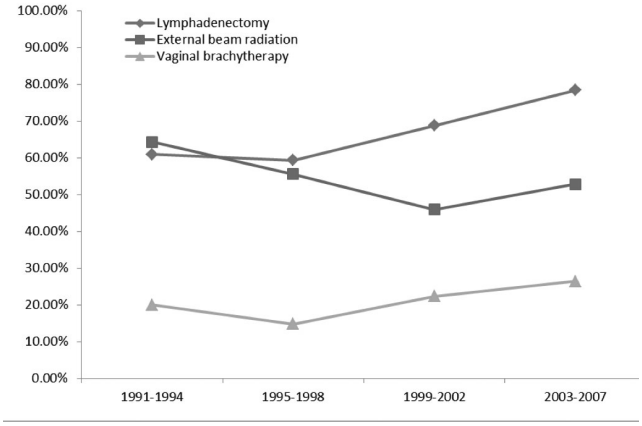

Figure 1. — Percentage of cases of Stage IB Grade 3 endometrial cancer that underwent lymphadenectomy, external beam radiation therapy or vaginal brachytherapy between years 1991 and 2007.

Clear cell adenocarcinoma and serous carcinoma were both rare, accounting for 2.7% and 9.3% of the study cohort, respectively. The geographic distributions of the patients were as follows: 22.4% from the northeast, 19.1% from the midwest, 11.1% from the south, and 47.4% from the west. A large portion (31.9%) of the patients had co-morbidities as determined by a modified Charlson co-morbidity index score equal to or greater than one (range 1-8). Lymphadenectomy was performed in 69.2% of the patients. Adjuvant EBRT was administered in 53.5% of the patients, and VBT in 22.1% patients. Only 6.9% of the patients received adjuvant chemotherapy.

Trends of adjuvant treatment in patients with stage IB grade 3 uterine cancer: Overall, the use of adjuvant chemotherapy increased significantly over time for patients with FIGO Stage IB Grade 3 endometrial cancer ($p < 0.001$; data not shown due to SEER-Medicare confidentiality rules, which suppresses cells with fewer than 11 patients). Similarly, there has been a trend towards an increased rate of performance of lymphadenectomy ($p < 0.001$) and administration of VBT ($p = 0.11$) over time in this patient population (Figure 1). In contrast, the administration of EBRT has decreased over time for patients with FIGO Stage IB Grade 3 endometrial cancer ($p = 0.02$; Figure 1).

Predictors of lymphadenectomy and adjuvant treatment: The authors used multivariable logistic regression to analyze the predictors of performance of lymphadenectomy and receipt of adjuvant treatment (Table 2). Age, area of residence, and co-morbidity score emerged as significant independent predictors of performance of lymphadenectomy. Women ≥ 80 years of age were less likely to undergo lymphadenectomy, as were those who had co-morbidities. Women diagnosed between years 2003-2007 were almost three times more likely to undergo lymphadenectomy compared to those diagnosed between years 1991-1994. Com-

Table1. — *Clinical and demographic characteristics of patients with Stage IB Grade 3 endometrial cancer.*

	Stage IB Grade 3 patients	
	N	%
Age (years)		
65-69	119	19.1
70-74	152	24.4
75-79	160	25.6
80-84	118	18.9
≥ 85	75	12.0
Race		
White	573	91.8
Black	23	3.7
Other/missing	28	4.5
Year of diagnosis		
1991-1994	115	18.4
1995-1998	108	17.3
1999-2002	170	27.2
2003-2007	231	37.1
Marital status		
Unmarried	366	58.7
Married	245	39.2
Unknown	13	2.1
Area of residence		
Rural	82	13.1
Urban	542	86.9
SEER registry		
Northeast	119	22.4
Midwest	140	19.1
South	69	11.1
West	296	47.4
**Median household income*		
First (lowest) tertile	275	44.1
Second tertile	197	31.6
Third (highest) tertile	152	24.3
***High-school education*		
First (lowest) tertile	177	28.4
Second tertile	216	34.6
Third (highest) tertile	231	37.0
Comorbidity score		
0	425	68.1
1	139	22.3
≥ 2	60	9.6
Histology		
Endometrioid	344	55.1
Adenocarcinoma NOS	205	32.9
Clear cell	17	2.7
Serous	58	9.3
Lymphadenectomy		
No	192	30.8
Yes	432	69.2
Chemotherapy		
No	581	93.1
Yes	43	6.9
External beam radiation		
No	290	46.5
Yes	334	53.5
Vaginal brachytherapy		
No	486	77.9
Yes	138	22.1

** Median household income level within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: < $40,000; Second tertile: $40,000– $60,000; Third (highest) tertile: > $60,000].*

*** Percentage of population with high-school education within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: 0– 21.8%; Second tertile: 21.8– 31.4%; Third (highest) tertile: 31.4– 55.8%].*

pared to patients residing in rural areas, patients living in the urban areas were twice as likely to undergo lymphadenectomy.

Age, histologic type, performance of lymphadenectomy, and receipt of VBT were the only significant predictors of receipt of chemotherapy. Age of 80 years or greater was associated with less use of chemotherapy. Patients with serous carcinoma and clear cell carcinoma were much more likely to be treated with chemotherapy compared to those diagnosed with endometrioid adenocarcinoma (OR 21.59, 95% CI: 7.37–63.26 and OR 10.66, 95% CI: 1.77–64.18, respectively). Similarly, those patients who underwent a lymphadenectomy or received adjuvant VBT were also more likely to be treated with chemotherapy compared to their respective counterparts. In analysis of predictors of treatment with EBRT, advanced age showed a significant negative association (Table 2). Women in the midwest region of the United States were more likely treated with adjuvant EBRT when compared to those residing in the northeast region. The negative predictors for receipt of VBT included advanced age, residence in the western region of the United States, and serous histologic type.

Association of therapies with survival: The median follow up was 51 (range: 12–215) months. The median overall survival for patients with Stage IB Grade 3 endometrial cancer in the current study was 91 (95% CI: 78–103) months. Initially, a univariate analysis was performed to determine the factors significantly associated with survival. Table 3 shows the five-year overall survival and cancer-specific survival among patients with FIGO Stage IB Grade 3 endometrial cancer according to different demographic and clinico-pathologic factors. The following factors were found to have a significant positive impact on overall survival: younger patient age ($p < 0.001$), non-black race ($p = 0.002$), later year of diagnosis ($p = 0.002$), married ($p = 0.007$), low co-morbidity score ($p < 0.001$), endometrioid or adenocarcinoma histology ($p = 0.001$), performance of lymphadenectomy ($p = 0.001$), and administration of EBRT ($p = 0.02$). When analyzing cancer-specific survival, following factors were found to be significant: non-black race ($p = 0.04$), low co-morbidity score ($p = 0.02$), and endometrioid or adenocarcinoma histology ($p < 0.001$).

Cox proportional hazards modeling was used to examine the influence of adjuvant therapy on overall survival and cancer-specific survival while accounting for other prognostic variables (Table 4). Adjuvant treatment with chemotherapy, EBRT, or VBT did not affect either overall survival or cancer-specific survival in patients with FIGO Stage IB Grade 3 endometrial cancer. Although, performance of lymphadenectomy was associated with a trend towards improved overall survival and cancer-specific survival, this was not statistically significant. Variables significantly associated with increased risk of all-cause death among patients with FIGO Stage IB Grade 3 endometrial cancer included advanced patient age, black race, presence

of co-morbidities, and non-endometrioid histologic types. Diagnosis in later years of study period (2003-2007) was associated with decreased overall mortality compared to earlier time period (1991-1994). When examining cancer-specific survival, only advanced age, black race, and serous histologic type were associated with an increased risk of cancer-specific death.

Discussion

Patients with FIGO Stage IB Grade 3 endometrial cancer represent a unique sub-group of patients. Both age, and race were found to be important prognostic factors as previously reported [10, 21]. There was poorer survival for women diagnosed with non-endometrioid histologies compared to those diagnosed with endometrioid type endometrial cancer. This is contrary to some reports that have suggested that outcome in patients with FIGO Grade 3 endometrioid cancer is similar to that observed in those diagnosed with serous and clear cell histologic types [22].

Significant controversy exists on how much adjuvant therapy is required in patients with surgical Stage I endometrial cancer. In the current study the authors sought to determine the impact of adjuvant therapy on survival in patients with FIGO Stage IB Grade 3 endometrial cancer. EBRT was the main-stay of adjuvant treatment, with approximately 54% patients receiving EBRT in the current study. VBT was administered in only 22% of the patients. Similar trends were reported in a survey study of practice patterns of the members of Society of Gynecologic Oncology in the United States [23].

EBRT has been shown to decrease loco-regional recurrence in early stage patients without any effect on overall survival [12, 13]. Furthermore, VBT has been shown to provide comparable reduction in vaginal recurrence as EBRT [17]. Given that pelvic recurrence rates are low among intermediate risk patients, VBT is considered the adjuvant treatment of choice in these patients. Since none of the PORTEC trials [13, 17] included high-risk patients with current FIGO Stage IB Grade 3 endometrial cancer, there is no evidence to support replacement of EBRT with VBT in these patients. In fact in the Norwegian trial that randomized patients with clinical Stage I endometrial cancer after hysterectomy and postoperative VBT to additional EBRT versus observation, the subgroup of patients with Grade 3 tumors and ≥ 50% myometrial invasion, showed a trend towards improved local control and survival after EBRT [24]. The current American Society of Radiation Oncology (ASTRO) guidelines also support the use of EBRT over VBT in this situation [25]. Unfortunately, the present authors were not able to demonstrate a survival benefit with the use of EBRT in these patients in the current study. Whether, pelvic recurrence rates are improved with EBRT or not, cannot be discerned from this study as the recurrence data were not available.

Multiple authors have reported that deep myometrial invasion and high tumor grade are independent predictors of distant relapse [5, 6, 26]. Despite the increased risk of distant recurrence, only 7% patients in the present study received adjuvant chemotherapy. This could be reflective of the older age of the study population and the concurrent co-morbidities. Indeed seen on multivariable analysis was a negative association between advanced age and receipt of chemotherapy. Additionally, although there was significantly more use of chemotherapy in treatment of non-endometrioid histologies compared to the endometrioid type, clear cell and serous uterine cancers accounted for only 3% and 10% of the study cohort, respectively.

The progression free survival and overall survival rates of FIGO Stage IB Grade 3 endometrial cancer have been shown to be strongly influenced by distant recurrence rates [26]. Chemotherapy is used in the adjuvant setting with a goal to lower the risk of distant metastasis and potentially improve overall survival. Although the effect of chemotherapy on distant relapse rate could not be determined in the current study, this study failed to show a survival benefit associated with the use of adjuvant chemotherapy in patients with FIGO Stage IB Grade 3 endometrial cancer. Similar results have been reported in various phase III clinical trials evaluating the role of chemotherapy in high-risk endometrial cancer [14-16]. A Japanese gynecologic oncology group study randomized patients with deeply invasive (> 50% myometrial invasion) endometrial cancer to chemotherapy *vs*. EBRT [15]. There was no difference between the chemotherapy and radiation arms in terms of progression free survival or overall survival. Only on post-hoc analysis did chemotherapy significantly improve progression free survival and overall survival in high to intermediate risk group, which included patients with current FIGO Stage IB Grade 3 endometrial cancer. The initial results of GOG249, which compared EBRT to chemotherapy plus VBT in patients with high-intermediate risk and high-risk endometrial cancer, also show comparable survival rates between groups, with no superiority of chemotherapy [27].

Almost 70% of the study cohort underwent a lymphadenectomy. As expected, older patients and those with co-morbidities were less likely to undergo a lymphadenectomy. Only including a sub-group of high-risk patients in the current study, the present studies were not able to demonstrate a survival benefit with the performance of lymphadenectomy. Lymphadenectomy has likewise not shown to be associated with improved survival in patients with early stage endometrial cancer in randomized controlled clinical trials [28, 29].

The major strength of the present study is the examination of a large number of patients with this relatively rare tumor from the SEER-Medicare database (n = 624). Because of the large sample size, the authors were able to perform a robust analysis to individually assess the impact of adjuvant treatment on survival in FIGO Stage IB Grade 3

Table 2. — *Multivariable logistic regression models of predictors of performance of lymphadenectomy and receipt of adjuvant chemotherapy, external beam radiation therapy, and vaginal brachytherapy among patients diagnosed with stage IB grade 3 endometrial cancer*

	Stage IB Grade 3 patients			
	Lymphadenectomy	Chemotherapy	External beam radiation therapy	Vaginal brachytherapy
Age (years)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
65-69	Referent	Referent	Referent	Referent
70-74	0.66 (0.36−1.21)	0.63 (0.23−1.73)	1.00 (0.58−1.71)	0.62 (0.35−1.10)
75-79	0.63 (0.34−1.14)	0.57 (0.19−1.71)	0.78 (0.46−1.33)	*0.38 (0.21−0.70)
80-84	*0.49 (0.26−0.94)	*0.15 (0.03−0.74)	*0.34 (0.19−0.61)	*0.44 (0.23−0.85)
≥ 85	*0.23 (0.11−0.48)	0.15 (0.02−1.46)	*0.10 (0.05−0.22)	*0.27 (0.11−0.64)
Race				
White	Referent	Referent	Referent	Referent
Black	0.54 (0.20−1.48)	0.48 (0.04−5.37)	1.83 (0.68−4.93)	2.64 (0.94−7.44)
Other	1.03 (0.38-2.82)	1.46 (0.22−9.62)	2.07(0.80−5.38)	1.33 (0.47−3.74)
Year of diagnosis				
1991-1994	Referent	Referent	Referent	Referent
1995-1998	0.83 (0.45−1.53)	—	0.77 (0.41−1.44)	0.73 (0.33−1.60)
1999-2002	1.38 (0.77−2.49)	0.84 (0.16−4.49)	0.60 (0.33−1.09)	1.16 (0.58−2.31)
2003-2007	*2.89 (1.53−5.47)	3.39 (0.71−16.29)	0.77 (0.41−1.44)	1.01 (0.49−2.07)
Marital status				
Unmarried	Referent	Referent	Referent	Referent
Married	1.00 (0.67−1.50)	0.87 (0.38−2.01)	1.28 (0.88−1.87)	0.93 (0.60−1.44)
Area of residence				
Rural	Referent	Referent	Referent	Referent
Urban	*2.02 (1.10−3.71)	0.56 (0.14−2.31)	0.92 (0.49−1.72)	0.53 (0.26−1.07)
SEER registry				
Northeast	Referent	Referent	Referent	Referent
Midwest	1.64 (0.86−3.11)	0.43 (0.10−1.73)	*2.56 (1.36−4.82)	0.82 (0.42−1.61)
South	1.11 (0.52−2.41)	0.29 (0.05−1.51)	1.16 (0.56−2.39)	0.48 (0.21−1.12)
West	1.71 (0.93−3.12)	0.73 (0.22−2.40)	1.52 (0.87−2.66)	*0.43 (0.23−0.80)
¶*Median household income*				
First (lowest) tertile	Referent	Referent	Referent	Referent
Second tertile	0.90 (0.57−1.43)	1.08 (0.35−3.36)	1.23 (0.78−1.92)	*1.81 (1.07−3.07)
Third (highest) tertile	1.72 (0.91−3.26)	1.18 (0.32−4.31)	1.47 (0.83−2.61)	1.34 (0.67−2.67)
¶¶*High-school education*				
First (lowest) tertile	Referent	Referent	Referent	Referent
Second tertile	0.87 (0.51−1.50)	0.86 (0.28−2.69)	1.51 (0.93−2.47)	1.04 (0.58−1.86)
Third (highest) tertile	0.63 (0.33−1.18)	1.52 (0.40−5.84)	1.62 (0.90−2.90)	0.89 (0.45−1.79)
Comorbidity score				
0	Referent	Referent	Referent	Referent
1	*0.58 (0.37−0.93)	1.52 (0.64−3.62)	0.77 (0.50−1.19)	0.81 (0.47−1.38)
≥ 2	0.56 (0.30−1.05)	—	1.13 (0.60−2.11)	1.69 (0.87−3.27)
Histology				
Endometrioid	Referent	Referent	Referent	Referent
Adenocarcinoma NOS	0.77 (0.48−1.21)	1.07 (0.30−3.85)	0.95 (0.61−1.49)	0.88 (0.52−1.48)
Clear cell	0.57 (0.19−1.71)	*10.66 (1.77−64.18)	1.94 (0.57−6.62)	0.33 (0.07−1.61)
Serous	0.72 (0.37−1.40)	*21.59 (7.37−63.26)	0.75 (0.39−1.44)	*0.35 (0.14−0.89)
Lymphadenectomy				
No	Referent	Referent	Referent	Referent
Yes	—	*5.39 (1.32−22.06)	0.78 (0.52−1.18)	1.28 (0.79−2.09)
Chemotherapy				
None	Referent	Referent	Referent	Referent
Yes	—	—	1.00 (0.47−2.16)	*3.35 (1.47−7.65)
External beam radiation				
No	Referent	Referent	Referent	Referent
Yes	—	0.91 (0.38−2.20)	—	—
Vaginal brachytherapy				
No	Referent	Referent	Referent	Referent
Yes	—	*3.57 (1.41−9.08)	—	—

*$p<0.05$

¶ *Median household income level within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: < $40,000; Second tertile: $40,000− $60,000; Third (highest) tertile: > $60,000].*

¶¶ *Percentage of population with high-school education within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: 0− 21.8%; Second tertile: 21.8− 31.4%; Third (highest) tertile: 31.4− 55.8%].*

Table 3. — *Univariable analysis of factors associated with overall survival and cancer-specific survival among patients diagnosed with Stage IB Grade 3 endometrial cancer.*

	5-year overall survival, %	*p*-value	5-year cause-specific survival, %	*p*-value
Age (years)		< 0.001		0.16
65-69	77.9%		82.5%	
70-74	67.0%		74.5%	
75-79	63.8%		77.3%	
80-84	62.4%		75.5%	
≥ 85	37.6%		63.4%	
Race		0.002		0.04
White	65.2%		76.3%	
Black	34.9%		60.0%	
Other	68.6%		75.1%	
Year of diagnosis		0.002		0.16
1991-1994	66.1%		79.7%	
1995-1998	51.9%		67.4%	
1999-2002	62.4%		75.0%	
2003-2007	76.4%		79.9%	
Marital status	0.007			0.48
Unmarried	59.7%		74.1%	
Married	71.0%		78.5%	
Area of residence		0.10		0.82
Rural	57.0%		74.9%	
Urban	64.9%		75.9%	
SEER registry		0.81		0.50
Northeast	69.0%		75.1%	
Midwest	58.4%		72.2%	
South	67.2%		78.9%	
West	64.3%		77.2%	
**Median household income*		0.14		0.11
First (lowest) tertile	58.3%		70.8%	
Second tertile	69.2%		80.6%	
Third (highest) tertile	67.7%		78.6%	
***High-school education*		0.92		0.64
First (lowest) tertile	62.8%		75.9%	
Second tertile	62.1%		75.2%	
Third (highest) tertile	66.8%		76.4%	
Comorbidity score		< 0.001		0.02
0	65.7%		75.5%	
1	66.5%		81.5%	
≥ 2	45.6%		65.2%	
Histology		0.001		< 0.001
Endometrioid	68.2%		78.5%	
Adenocarcinoma NOS	64.1%		78.5%	
Clear cell	52.3%		65.4%	
Serous	41.5%		50.4%	
Lymphadenectomy		0.001		0.07
No	55.8%		73.1%	
Yes	67.8%		77.0%	
Chemotherapy		0.54		0.35
No	63.9%		76.2%	
Yes	67.6%		69.8%	
External beam radiation		0.02		0.67
No	60.3%		77.2%	
Yes	67.1%		74.7%	
Vaginal brachytherapy		0.07		0.25
No	62.1%		75.1%	
Yes	70.9%		78.3%	

** Median household income level within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: <$40,000; Second tertile: $40,000−$60,000; Third (highest) tertile: >$60,000]*

*** Percentage of population with high-school education within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: 0−21.8%; Second tertile: 21.8−31.4%; Third (highest) tertile: 31.4−55.8%]*

Table 4. — *Multivariable cox proportional hazards models of overall survival and cancer-specific survival among patients diagnosed with Stage IB Grade 3 endometrial cancer.*

	Stage IB Grade 3	
	Overall survival	Cancer specific survival
Age (years)		
65-69	Referent	Referent
70-74	1.02 (0.67−1.55)	1.19 (0.68−2.06)
75-79	*1.69 (1.12−2.54)	1.34 (0.77−2.35)
80-84	*1.69 (1.10−2.59)	1.30 (0.71−2.38)
≥ 85	*3.56 (2.18−5.82)	*2.77 (1.40−5.48)
Race		
White	Referent	Referent
Black	*3.71 (1.97−6.96)	*2.58 (1.12−5.94)
Other	1.43 (0.78−2.63)	1.69 (0.79−3.60)
Year of diagnosis		
1991-1994	Referent	Referent
1995-1998	1.33 (0.94−1.89)	1.71 (1.00−2.90)
1999-2002	0.82 (0.57−1.18)	0.97 (0.57−1.65)
2003-2007	*0.48 (0.30−0.77)	0.77 (0.42−1.41)
Marital status		
Unmarried	Referent	Referent
Married	0.95 (0.73−1.24)	1.09 (0.75−1.57)
Area of residence		
Rural	Referent	Referent
Urban	0.88 (0.58−1.33)	1.57 (0.86−2.87)
SEER registry		
Northeast	Referent	Referent
Midwest	0.97 (0.63−1.49)	0.83 (0.47−1.46)
South	0.83 (0.46−1.51)	0.65 (0.30−1.40)
West	1.03 (0.69−1.54)	0.69 (0.40−1.18)
¶*Median household income*		
First (lowest) tertile	Referent	Referent
Second tertile	0.90 (0.66−1.22)	0.65 (0.42−1.01)
Third (highest) tertile	0.92 (0.61−1.38)	0.69 (0.40−1.20)
¶¶*High-school education*		
First (lowest) tertile	Referent	Referent
Second tertile	0.74 (0.52−1.04)	0.76 (0.46−1.24)
Third (highest) tertile	1.01 (0.68−1.51)	1.10 (0.63−1.91)
Comorbidity score		
0	Referent	Referent
1	0.89 (0.64−1.23)	0.62 (0.38−1.01)
≥ 2	*2.42 (1.67−3.52)	1.65 (0.97−2.81)
Histology		
Endometrioid	Referent	Referent
Adenocarcinoma NOS	0.95 (0.71−1.27)	0.94 (0.62−1.41)
Clear cell	*2.15 (1.10−4.22)	1.60 (0.62−4.12)
Serous	*2.39 (1.51−3.76)	*2.94 (1.69−5.11)
Lymphadenectomy		
No	Referent	Referent
Yes	0.86 (0.66−1.11)	0.83 (0.58−1.19)
Chemotherapy		
No	Referent	Referent
Yes	1.30 (0.64−2.66)	1.36 (0.61−3.05)
External beam radiation		
No	Referent	Referent
Yes	0.94 (0.71−1.22)	1.33 (0.91−1.93)
Vaginal brachytherapy		
No	Referent	Referent
Yes	0.84 (0.60−1.17)	0.73 (0.46−1.16)

*$p < 0.05$

¶ *Median household income level within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: <$40,000; Second tertile: $40,000−$60,000; Third (highest) tertile: >$60,000]*

¶¶ *Percentage of population with high-school education within the census tract in which the patient resided at the time of diagnosis [First (lowest) tertile: 0−21.8%; Second tertile: 21.8−31.4%; Third (highest) tertile: 31.4−55.8%].*

endometrial cancer. Several limitations of this study must be acknowledged. First, the authors lacked data on performance status. Second, given that lymph node dissection was not performed in all patients, understaging is possible. There is some suggestion that patients with incomplete surgical staging are more likely to be offered adjuvant treatment [30]. This could result in an over-representation of understaged patients in the adjuvant treatment group and a false underestimate of the adjuvant treatment-related survival benefit. Third, the present authors included only patients at least 65 years of age, so the results may not be generalizable to younger patients. Fourth, this study did not include patients diagnosed after 2007. More recently diagnosed patients were excluded to ensure sufficient follow-up to assess the association of treatment with survival. Fifth, although the use of chemotherapy was recorded, details regarding the chemotherapy cycles and dosing were not available. Similarly, data regarding radiation techniques such as treatment fields, dose, and fractionation were not included. Sixth, the SEER database's lack of important information regarding disease recurrence precluded an analysis of patterns of failure and progression free survival. Although clinically relevant, progression free survival does not adequately measure the impact of post-recurrence therapy on survival. Finally, unlike randomized trials, decisions about treatment are based on many uncontrolled and unknown factors in a real-world setting, which may have influenced the observed treatment-related outcomes.

Conclusion

In summary, patients with FIGO Stage IB Grade 3 endometrial cancer represent a unique sub-group of patients. Prognosis is significantly worse in patients diagnosed with non-endometrioid histologies compared to those diagnosed with the more common endometrioid type endometrial cancer. EBRT appears to the most commonly used modality for adjuvant treatment in these patients. However, the use of adjuvant chemotherapy and VBT in this setting has increased over time. Although, the current study does not seek to define treatment recommendations, there appears to be no beneficial impact of adjuvant radiation or chemotherapy on overall survival or cancer-specific survival in patients with FIGO Stage IB Grade 3 endometrial cancer.

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