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Original Article

Management of stage II endometrial cancer and subsequent oncologic outcomes: a National Cancer Database study

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ABSTRACT

Objective: The management of stage II endometrial cancer (EC) is challenging due to the wide variation in surgical practice and adjuvant treatment recommendations. We sought to describe the treatment patterns for patients with stage II EC and to evaluate the association between surgical management and adjuvant therapy on survival outcomes in a large cohort of patients with stage II EC.
Methods: Using data from the National Cancer Database, we identified 9,690 women with stage II EC. We used logistic regression to identify association of sociodemographic and tumor characteristics with surgery type and receipt of adjuvant therapy. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between adjuvant therapy, hysterectomy type, and overall survival.
Results: Almost 11% of the cohort underwent radical hysterectomy; however, there was no difference in survival between surgical types even when adjusted for adjuvant therapy (HR=0.94; 95% CI=0.82–1.07). Compared to no adjuvant treatment, radiation only (HR=0.66; 95% CI=0.61–0.73) and combination radiation and chemotherapy (HR=0.53; 95% CI=0.45–0.62) were associated with lower risk of death. There was no survival benefit of chemotherapy alone even when separated by histologic subtype (HR range, 0.55–1.46).
Conclusions: Women with stage II EC do not appear to benefit from routine radical hysterectomy though all patients appear to benefit from receipt of radiation therapy (RT), regardless of modality. Additionally, there may be an added survival benefit with the combination of computed tomography and RT in patients with non-endometrioid, high-risk histologies.

Keywords: Endometrial Cancer; Radiation Therapy; Hysterectomy; Intracavity Radiotherapy; Adjuvant Chemotherapy

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States with approximately 60,000 new diagnoses per year [1]. Comprehensive surgical staging is the cornerstone of management providing both risk stratification to determine need for adjuvant therapy and therapeutic benefit for early-stage EC. The first surgical staging system was developed in 1988 by the International Federation of Gynecology and Obstetrics (FIGO)

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

Author Contributions
Conceptualization: F.A.S.; Data curation: V.M.H., F.A.S.; Formal analysis: V.M.H., B.K., F.A.S.; Investigation: V.M.H., B.K., F.A.S.; Methodology: F.A.S.; Project administration: V.M.H., F.A.S.; Resources: V.M.H., F.A.S.; Software: F.A.S.; Supervision: B.K., F.A.S.; Validation: V.M.H., F.A.S.; Writing - original draft: V.M.H., B.K., F.A.S.; Writing - review & editing: V.M.H., B.K., F.A.S.

and defined stage II EC as involvement of either the cervical mucosa or stroma [2]. According to the 2006 FIGO report on uterine cancer, 12% of patients present with stage II disease [3]. However, since this time, the staging system was further refined and involvement of the endocervical glands was removed from the definition of stage II disease due to lack of prognostic implications [4-6].

Historically, patients with gross cervical involvement underwent radical hysterectomy with lymph node assessment [7,8]. However, recent data suggest a lack of benefit of routine radical hysterectomy for patients with stage II EC [9,10]. This ambiguity is reflected in the National Comprehensive Cancer Network (NCCN) Guidelines that recommend either extrafascial or radical hysterectomy for patients with suspected or gross cervical involvement and endometrioid histology [8]. Furthermore, the European Society of Medical Oncology-European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Gynecological Oncology (ESGO) consensus conference on EC recommended against radical hysterectomy for management of stage II EC with a B strength recommendation [11].

Use of adjuvant therapy following surgical management also remains controversial. Again, this variability is reflected in the current NCCN endometrial carcinoma guidelines where a wide range of treatment options are recommended [8]. Historically, adjuvant radiation has been recommended for patients with stage II disease based on the results of several large randomized trials including Gynecological Oncology Group (GOG) 99 and ASTEC/NCIC CTG EN.5 trials in which radiation was demonstrated to be superior to observation in patients with stage I–II disease [12,13]. Subsequent studies of use of vaginal brachytherapy (VBT) demonstrating comparable outcomes with external beam radiation therapy (EBRT) excluded women with cervical stromal involvement and are therefore may not be applicable for patients with FIGO 2009 stage II disease [14]. Adjuvant chemotherapy has been recommended for patients with high-grade/high-risk histologies, though these recommendations have typically been based on either small, single institution studies or small subgroup analyses of large trials [15-20].

Given the wide variation of treatment options for patients with FIGO 2009 stage II EC and the lack of studies including these patients, the purpose of this study was two-fold: First, we sought to describe treatment patterns for women with stage II EC. Secondly, we wanted to evaluate the impact of type of surgery as well as the effects of adjuvant therapy on survival outcomes in a large cohort of patients with stage II EC.

MATERIALS AND METHODS

1. Data source

Full details regarding the National Cancer Database (NCDB) have been published elsewhere [21]. Briefly, the NCDB is a nationwide, hospital-based cancer registry jointly sponsored by the American Cancer Society and the American College of Surgeons. The NCDB collects data from more than 1,500 Commission on Cancer (CoC)-accredited facilities in the United States and is thought to represent approximately 70% new cancer diagnoses per year [22]. The NCDB contains standardized information on sociodemographic characteristics, tumor characteristics, comorbidities, and attributes of the facility in which patients were treated. Currently, CoC facilities annually report vital status and date of death to the NCDB. All data are de-identified, and the study was considered exempt by the Ohio State University Institutional Review Board (IRB).

2. Study population

Between 2004 and 2015, 443,680 uterine cancers were recorded in the NCDB, of which, 332,266 women had an endometrial carcinoma or carcinosarcoma diagnosis and non-missing American Joint Committee on Cancer (AJCC) stage. We used International Classification of Diseases (ICD)-10 morphology codes to classify carcinomas or carcinosarcomas as endometrioid adenocarcinoma (8140, 8210, 8211, 8260–8263, 8380–8383, 8480–8482, 8560, and 8570), serous (8441, 8460–8461), carcinosarcoma (8950–8951, 8980–8981), clear cell (8310), and mixed epithelial (8255, 8323). Endometrioid adenocarcinoma tumors were further classified as low-grade (grades 1 or 2) or high-grade (grade 3). By definition, serous, carcinosarcoma, clear cell, and mixed epithelial histologies are considered poorly differentiated tumors; therefore, additional categorization based on grade was unnecessary [23].

Fig. 1 illustrates the study scheme. We excluded women with in situ (n=2,979), stage I (n=241,083), stage III (n=46,202), or stage IV (n=19,370) disease. We additionally excluded women with stages II or IIA disease as coded by the AJCC Sixth Edition (n=5,640), stages II

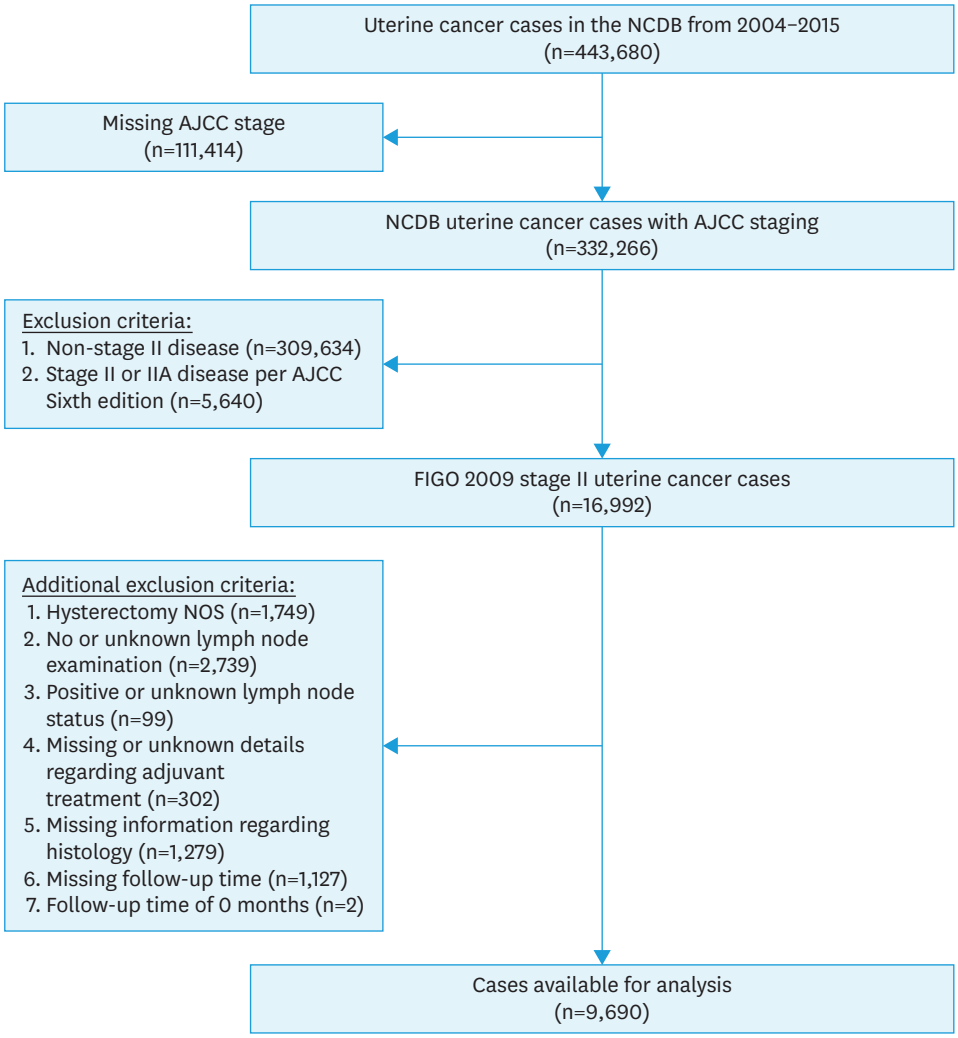

Fig. 1. Study scheme.
AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics; NCDB, National Cancer Database.

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(n=1,189) or IIA (n=4,451) disease with unknown AJCC Edition (n=5), hysterectomy, NOS (n=1,749), no regional lymph node examination or unknown if lymph node exam performed (n=2,739), positive or unknown lymph node status (n=99), treatment with radioisotopes, NOS or unknown radiation status (n=193), unknown chemotherapy (n=109), ungraded endometrioid histology (n=1,120), other histology (n=159), missing follow-up time (n=1,127), or follow-up time of 0 months (n=2) leaving 9,690 patients for analysis.

3. Study variables

We used the Participant User Files (PUF), a publicly shared subset of the NCDB. All variables were captured using standardized codes defined by the Facility Oncology Registry Data Standards (FORDS). We included information on age at diagnosis (<60, ≥60 years), race (white, black, Hispanic, other), pre-existing medical conditions as defined by the Charlson/Deyo index (0, 1, 2, ≥3), insurance status (uninsured, private insurance, Medicaid, Medicare, other government), facility location (Northeast, South Atlantic, Midwest, Mountain, Pacific), facility type (Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, Integrated Network Cancer Program), year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2015), histological subtype (low-grade endometrioid, high-grade endometrioid, serous, carcinosarcoma, clear cell, mixed epithelial), lymphovascular space invasion (no, yes), surgery (extrafascial/total hysterectomy, radical hysterectomy), chemotherapy (no, yes), radiation (no, yes), type of radiation (none, VBT, EBRT, combination EBRT and VBT), combination radiation and chemotherapy (none, chemotherapy only, radiation only, radiation and chemotherapy). Overall survival (OS) was calculated from the date of diagnosis to the date of death. Patients were otherwise censored at the date of last contact, whichever occurred first. Participants diagnosed in 2015 were excluded from survival analyses.

4. Statistical analysis

We examined distributions of sociodemographic and tumor characteristics according to type of hysterectomy using χ^2 tests. Missing values for sociodemographic and tumor characteristics were included as separate categories. Logistic regression was used to estimate odds ratios and 95% confidence intervals (CIs) for associations between age, lymphovascular space invasion (LVSI), and histology with receipt of adjuvant treatment. We used separate Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for associations between OS and 1) adjuvant treatment (none, chemotherapy only, radiation only, chemotherapy plus radiation) and 2) the joint effect of hysterectomy type and adjuvant radiation treatment. Variables were included as potential confounders if the factor was significantly associated with treatment and OS in univariable models. All confounders were categorized as presented in **Table 1**. We examined the proportional hazards assumption through inspection of the Wald *P* value for an interaction term including key exposures

Table 1. Characteristics of 9,690 women with stage II endometrial cancer overall and by type of primary surgery, National Cancer Database, 2004–2015

Characteristic	Overall (n=9,690)	Extrafascial hysterectomy (n=8,633)	Radical hysterectomy (n=1,057)	p*
Age (yr)				<0.001
<60	3,625 (37.4)	3,149 (36.5)	476 (45.0)	
≥60	6,065 (62.6)	5,484 (63.5)	581 (55.0)	
Race				0.305
White	8,029 (82.9)	7,140 (82.7)	889 (84.1)	
Black	1,127 (11.6)	1,021 (11.8)	106 (10.0)	
Other	412 (4.2)	362 (4.2)	50 (4.7)	
Unknown	122 (1.3)	110 (1.3)	12 (1.1)	

(continued to the next page)

Table 1. (Continued) Characteristics of 9,690 women with stage II endometrial cancer overall and by type of primary surgery, National Cancer Database, 2004–2015

Characteristic	Overall (n=9,690)	Extrafascial hysterectomy (n=8,633)	Radical hysterectomy (n=1,057)	p*
Charlson-Deyo score				0.483
0	7,256 (74.9)	6,469 (74.9)	787 (74.5)	
1	2,005 (20.7)	1,774 (20.6)	231 (21.8)	
2	353 (3.6)	322 (3.7)	31 (2.9)	
≥3	76 (0.8)	68 (0.8)	8 (0.8)	
Insurance status				<0.001
No insurance	448 (4.6)	376 (4.4)	72 (6.8)	
Private insurance	4,384 (45.2)	3,880 (45.0)	504 (47.7)	
Medicaid	521 (5.4)	458 (5.3)	63 (6.0)	
Medicare	4,122 (42.5)	3,735 (43.3)	387 (36.6)	
Other government	95 (1.0)	82 (1.0)	13 (1.2)	
Unknown	120 (1.2)	102 (1.2)	18 (1.7)	
Facility location				<0.001
Northeast	2,263 (23.4)	2,091 (24.2)	172 (16.3)	
South Atlantic	3,158 (32.6)	2,798 (32.4)	360 (34.1)	
Midwest	2,535 (26.2)	2,225 (25.8)	310 (29.3)	
Mountain	375 (3.9)	316 (3.7)	59 (5.6)	
Pacific	1,135 (11.7)	1,014 (11.8)	121 (11.4)	
Unknown	224 (2.3)	189 (2.2)	35 (3.3)	
Facility type				<0.001
Community cancer program	443 (4.6)	401 (4.6)	42 (4.0)	
Comprehensive community cancer program	3,726 (38.4)	3,321 (38.5)	405 (38.3)	
Academic/research program	4,161 (42.9)	3,749 (43.4)	412 (39.0)	
Integrated network cancer program	1,136 (11.7)	973 (11.3)	163 (15.4)	
Unknown	224 (2.3)	189 (2.2)	35 (3.3)	
Year of diagnosis				0.757
2004–2006	2,028 (20.9)	1,804 (20.9)	224 (21.2)	
2007–2009	2,368 (24.4)	2,113 (24.5)	255 (24.1)	
2010–2012	3,117 (32.2)	2,765 (32.0)	352 (33.3)	
2013–2015	2,177 (22.5)	1,951 (22.6)	226 (21.4)	
Histology				<0.001
Low-grade endometrioid	5,218 (53.8)	4,730 (54.8)	488 (46.2)	
High-grade endometrioid	1,680 (17.3)	1,440 (16.7)	240 (22.7)	
Serous	907 (9.4)	826 (9.6)	81 (7.7)	
Carcinosarcoma	710 (7.3)	632 (7.3)	78 (7.4)	
Clear cell	314 (3.2)	266 (3.1)	48 (4.5)	
Mixed epithelial	861 (8.9)	739 (8.6)	122 (11.5)	
Lymphovascular space invasion				0.123
No	3,180 (32.8)	2,857 (33.1)	323 (30.6)	
Yes	1,651 (17.0)	1,478 (17.1)	173 (16.4)	
Unknown	4,859 (50.1)	4,298 (49.8)	561 (53.0)	
Chemotherapy				0.002
No	8,308 (85.7)	7,435 (86.1)	873 (82.6)	
Yes	1,382 (14.3)	1,198 (13.9)	184 (17.4)	
Radiation				<0.001
No	3,107 (32.1)	2,678 (31.0)	429 (40.6)	
Yes	6,583 (67.9)	5,955 (69.0)	628 (59.4)	
Radiation type				<0.001
None	3,107 (32.1)	2,678 (31.0)	429 (40.6)	
Brachytherapy	2,665 (27.5)	2,422 (28.1)	243 (23.0)	
External beam radiation	1,555 (16.1)	1,415 (16.4)	140 (13.2)	
Combination external beam and brachytherapy	2,363 (24.4)	2,118 (24.5)	245 (23.2)	
Combination radiation and chemotherapy				<0.001
None	2,704 (27.9)	2,336 (27.1)	368 (34.8)	
Chemotherapy only	403 (4.2)	342 (4.0)	61 (5.8)	
Radiation only	5,604 (57.8)	5,099 (59.1)	505 (47.8)	
Radiation and chemotherapy	979 (10.1)	856 (9.9)	123 (11.6)	

*p-value compares extrafascial hysterectomy and radical hysterectomy.

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(hysterectomy type, adjuvant treatment, etc.) and log follow-up time. All analyses were conducted using SAS software (version 9.4; SAS Statistical Institute, Cary, NC, USA).

RESULTS

1. Study population characteristics: overall and according to type of hysterectomy

Table 1 describes the distribution of patient characteristics and clinical factors in the overall cohort and according to type of hysterectomy. Of the 9,690 women with stage II EC included in the study, 62.6% of patients were at least 60 years of age,82.9% were white (82.9%) with Charlson-Deyo score of 0 (74.9%). Fifty-five percent of patients were diagnosed between 2010 and 2014 (54.7%) and treated at either a comprehensive community cancer program (38.4%) or at academic/research program (42.9%). The most commonly reported histologic subtype was low-grade endometrioid (53.8%) followed by high-grade endometrioid (17.3%). There were approximately 1,000 cases of both serous (9.4%) and mixed-epithelial EC (8.9%) included in this analysis. Carcinosarcomas and clear cell ECs were rare, representing 7.3% and 3.2% of the cohort respectively. LVSI was unknown in approximately half of the cohort. Extrafascial hysterectomy was more commonly performed than radical hysterectomy (89.1% vs. 10.9%, respectively).

Over 2,700 patients received no adjuvant therapy (27.9%). Radiation was more commonly used in this cohort (67.9%) compared to chemotherapy (14.3%). When radiation was utilized, brachytherapy was the most frequently used modality (27.5%) followed by combination of external beam and brachytherapy (24.4%). Finally, the combination of both chemotherapy and radiation was uncommon in this cohort with only 10.1% of participants receiving both modalities while only 4.2% of patients received chemotherapy alone.

Patient and clinical characteristics differed between women undergoing radical versus extrafascial hysterectomy. High-grade endometrioid tumors and mixed epithelial tumors were more common in the radical hysterectomy group compared to the extrafascial group (22.7% vs. 16.7% and 11.5% vs. 8.6%, $p<0.001$). A higher proportion of patients received no adjuvant therapy in the radical hysterectomy group compared to the extrafascial hysterectomy group (34.8% vs. 27.1%, $p<0.001$). Receipt of chemotherapy was higher in the radical hysterectomy group (17.4% vs. 13.9%, $p<0.001$) while receipt of radiation was higher in the extrafascial hysterectomy group (69.0% vs. 59.4%).

2. Correlates of adjuvant therapy

When compared to younger women, older women were less likely to receive radiation alone (OR for each one-year increase in age 0.80; 95% CI=0.73–0.89) or chemotherapy alone (OR=0.66; 95% CI=0.52–0.83). Lower odds of receiving only radiation were observed among women with serous (OR=0.58; 95% CI=0.48–0.69) or carcinosarcoma histology (OR=0.53; 95% CI=0.44–0.63) compared with low-grade endometrioid. Women with a diagnosis of high-grade histologies (compared to low-grade endometrioid, ORs range between 3.59 and 12.43) had higher odds of receiving only chemotherapy. Patients with high-grade endometrioid histologies were more likely to receive chemotherapy or chemotherapy plus radiation than their low-grade counterparts (OR=1.96; 95% CI=1.36–2.82; OR=3.59; 95% CI=2.84–4.52) while there was no difference between use of radiation (OR=0.93; 95% CI=0.82–1.06).

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Table 2. HRs and 95% CIs for associations between surgery type, adjuvant treatment and overall survival among women with stage II endometrial cancer, National Cancer Database, 2004–2015

Variables	Deaths (%)	Unadjusted HR (95% CI)	HR (95% CI) adjusted for demographic factors*	HR (95% CI) adjusted for demographic factors and tumor and treatment characteristics†
Surgery				
Extrafascial hysterectomy	2,187 (25.3)	1.00	1.00	1.00
Radical hysterectomy	250 (23.6)	0.94 (0.82–1.07)	1.02 (0.89–1.16)	0.93 (0.81–1.06)
Adjuvant treatment				
None	849 (31.4)	1.00	1.00	1.00
Chemotherapy only	136 (33.7)	1.19 (0.99–1.42)	1.18 (0.98–1.41)	0.90 (0.75–1.09)
Radiation only	1,239 (22.1)	0.59 (0.54–0.65)	0.64 (0.59–0.70)	0.66 (0.61–0.73)
Radiation and chemotherapy	213 (21.8)	0.68 (0.58–0.79)	0.69 (0.59–0.81)	0.53 (0.45–0.62)

CI, confidence interval; HR, hazard ratio.
*HRs and 95% CIs adjusted for: age at diagnosis (<60, ≥60 years), race (white, black, Hispanic, other), pre-existing medical conditions (0, 1, 2, ≥3), insurance status (uninsured, private insurance, Medicaid, Medicare, other government, other), facility location (Northeast, South Atlantic, Midwest, Mountain, Pacific), year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2014); †HRs and 95% CIs additionally adjusted for: histological subtype (low-grade endometrioid, high-grade endometrioid, serous, carcinosarcoma, clear cell, mixed epithelial), lymphovascular space invasion (no, yes), surgery (extrafascial hysterectomy, radical hysterectomy), and adjuvant treatment (none, chemotherapy only, radiation only, radiation and chemotherapy).

3. Oncologic outcomes associated with treatment

The 5-year OS in this cohort was 75%. Associations between surgery type and adjuvant treatment in Cox regression models progressively adjusted for demographic factors, tumor characteristics, and adjuvant therapy are provided in **Table 2**. We observed no difference in survival associated with type of surgery in the fully-adjusted model (HR=0.93; 95% CI=0.81–1.06). Compared to no adjuvant treatment, radiation only (HR=0.66; 95% CI=0.61–0.73) and combination radiation and chemotherapy (HR=0.53; 95% CI=0.45–0.62) were associated with lower risk of all-cause mortality. When compared to radiation alone, use of the combination of radiation and chemotherapy was associated with a lower risk of death (HR=0.80; 95% CI=0.68–0.93).

We also compared the joint effects of surgery type (extrafascial vs. radical) and radiation type (none, EBRT, VBT, EBRT plus VBT) in Cox regression models progressively adjusted for demographic factors, tumor characteristics, and chemotherapy (**Table 3**). In the fully-adjusted model, there was again no difference in all-cause mortality between surgery types

Table 3. Multivariable-adjusted HRs and 95% CIs for the joint effect of surgery and radiation on overall survival among women with stage II endometrial cancer, National Cancer Database, 2004–2015

Variables	Deaths (%)	HR (95% CI)*	p	HR (95% CI) adjusted for demographic factors†	p	HR (95% CI) adjusted for demographic factors and tumor and treatment characteristics‡	p
Surgery and radiation			<0.001		<0.001		<0.001
Extrafascial hysterectomy only	856 (32.0)	1.00		1.00		1.00	
Extrafascial hysterectomy and EBRT	383 (27.1)	0.74 (0.66–0.83)		0.78 (0.69–0.88)		0.78 (0.69–0.88)	
Extrafascial hysterectomy and VBT	459 (19.0)	0.51 (0.45–0.57)		0.56 (0.50–0.62)		0.59 (0.53–0.67)	
Extrafascial hysterectomy and combination EBRT/VBT	489 (23.1)	0.58 (0.52–0.65)		0.63 (0.57–0.71)		0.66 (0.59–0.74)	
Radical hysterectomy only	129 (30.1)	0.90 (0.75–1.08)		1.01 (0.84–1.22)		1.00 (0.83–1.20)	
Radical hysterectomy and EBRT	28 (20.0)	0.55 (0.38–0.80)		0.63 (0.43–0.92)		0.62 (0.43–0.91)	
Radical hysterectomy and VBT	43 (17.7)	0.50 (0.36–0.67)		0.61 (0.45–0.84)		0.60 (0.44–0.82)	
Radical hysterectomy and combination EBRT/VBT	50 (20.4)	0.50 (0.38–0.67)		0.57 (0.43–0.76)		0.53 (0.40–0.71)	

CI, confidence interval; EBRT, external beam radiation therapy; HR, hazard ratio; VBT, vaginal brachytherapy.
*Unadjusted HR and 95% CI; †HRs and 95% CIs adjusted for demographic characteristics: age at diagnosis (<60, ≥60 years), race (white, black, Hispanic, other), pre-existing medical conditions (0, 1, 2, ≥3), insurance status (uninsured, private insurance, Medicaid, Medicare, other government, other), facility location (Northeast, South Atlantic, Midwest, Mountain, Pacific), year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2014); ‡HRs and 95% CIs additionally adjusted for tumor and treatment characteristics: histological subtype (low-grade endometrioid, high-grade endometrioid, serous, carcinosarcoma, clear cell, mixed epithelial), lymphovascular space invasion (no, yes), and chemotherapy (no, yes).

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but a benefit of receipt all types of radiation modalities was noted regardless of surgery type (HRs range between 0.53 and 0.78). Further, we conducted a direct comparison of extrafascial hysterectomy plus EBRT, VBT, and combination EBRT/VBT compared to radical hysterectomy alone and observed significantly lower risk of death associated with extrafascial hysterectomy and EBRT (HR=0.78; 95% CI=0.64–0.96), extrafascial hysterectomy and VBT (HR=0.60; 95% CI=0.49–0.73) and extrafascial hysterectomy and combination EBRT/VBT (HR=0.66; 95% CI=0.55–0.81).

Fig. 2 demonstrates the histology-stratified association of adjuvant treatment and survival. A lower risk of death was noted in all histologic subtypes with receipt of radiation plus chemotherapy (HRs range between 0.27 and 0.57). This association was most strongly noted in the patients with clear cell histology (HR=0.27; 95% CI=0.12–0.62). Patients with low-grade endometrioid (HR=0.61; 95% CI=0.53–0.71), high-grade endometrioid (HR=0.66; 95% CI=0.55–0.80), serous (HR=0.61; 95% CI=0.46–0.80), and mixed epithelial (HR=0.70; 95% CI=0.50–0.97) EC also appeared to derive a survival benefit with receipt of radiation alone. There was no survival benefit of use of chemotherapy alone in any histology group (HRs range between 0.55 and 1.46).

Adjuvant treatment	Deaths (%)	HR (95% CI)	p
Low-grade endometrioid (n=5,218)			<0.001
None	331 (22.2)	1.00	
RT only	531 (15.4)	0.61 (0.53–0.71)	
CT only	22 (25.6)	1.46 (0.94–2.27)	
RT+CT	19 (10.3)	0.57 (0.36–0.91)	
High-grade endometrioid (n=1,680)			<0.001
None	184 (40.1)	1.00	
RT only	316 (32.2)	0.66 (0.55–0.80)	
CT only	16 (31.4)	0.87 (0.52–1.46)	
RT+CT	44 (23.2)	0.59 (0.42–0.83)	
Serous (n=907)			<0.001
None	111 (46.4)	1.00	
RT only	104 (34.9)	0.61 (0.46–0.80)	
CT only	39 (34.8)	0.75 (0.51–1.09)	
RT+CT	72 (27.9)	0.51 (0.37–0.70)	
Carcinosarcoma (n=710)			0.002
None	128 (54.5)	1.00	
RT only	134 (49.4)	0.78 (0.60–1.00)	
CT only	37 (51.4)	1.05 (0.71–1.55)	
RT+CT	43 (32.6)	0.53 (0.36–0.76)	
Clear cell (n=314)			0.014
None	33 (39.8)	1.00	
RT only	52 (37.1)	0.81 (0.50–1.31)	
CT only	8 (30.8)	0.55 (0.24–1.23)	
RT+CT	8 (12.3)	0.27 (0.12–0.62)	
Mixed epithelial (n=861)			0.034
None	62 (32.0)	1.00	
RT only	102 (22.1)	0.70 (0.50–0.97)	
CT only	14 (25.0)	0.88 (0.48–1.62)	
RT+CT	27 (18.0)	0.53 (0.33–0.85)	

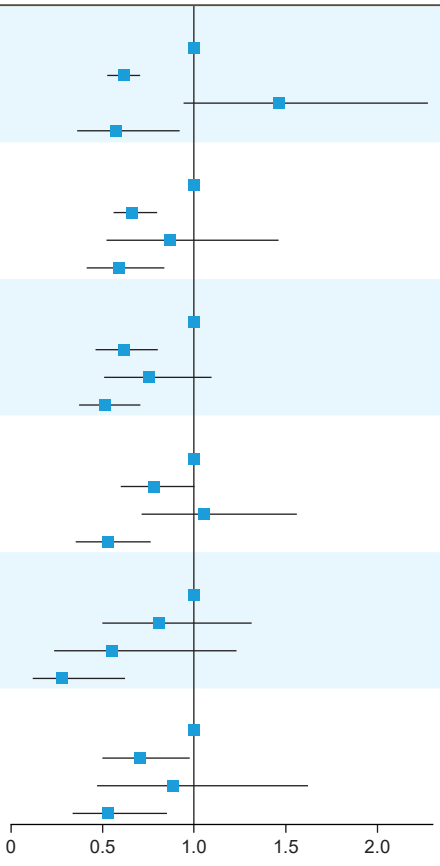

Fig. 2. Histology-stratified association of adjuvant treatment and survival.
CI, confidence interval; CT, computed tomography; HR, hazard ratio; RT, radiation therapy.

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DISCUSSION

Stage II EC is rare, representing less than 12% of all cases of EC [3]. Guidelines for treatment have either been extrapolated from small, retrospective cohort studies or from subgroup analyses of larger clinical trials. Additionally, many older studies utilize the 1988 FIGO staging guidelines including patients with cervical mucosal involvement as stage II, which we now know does not have prognostic implications.

Our data demonstrate that most patients with stage II disease undergo extrafascial hysterectomy (up to 90%) and receiving some type of radiation therapy (RT; up to 68%). One of the major questions regarding the management of stage II EC is the oncologic benefit of radical surgery. Several studies previously demonstrated improved survival with radical hysterectomy though these were small retrospective studies and included patients with cervical mucosal involvement [4,24]. In a more recent study by the Gynecologic Oncology Trial and Investigation Consortium of North Kanto (GOTIC), there were no differences in progression-free or OS between patients with pathologically-confirmed stage II disease who received extrafascial vs. radical hysterectomy [9]. Furthermore, a systemic review of 10 retrospective cohort studies of 2866 patients again did not demonstrate an OS (pooled HR=0.92; 95% CI=0.72–1.16) or progression-free survival benefit (pooled HR=0.75; 95% CI=0.39–1.42) [10]. This lack of survival benefit remained constant even when adjusting for radiation therapy.

Our study is consistent with these most recent studies as we did not demonstrate a benefit of radical hysterectomy even when adjusting for adjuvant therapy. Additionally, we found a lower risk of death in patients undergoing extrafascial hysterectomy plus any type of radiation compared to those undergoing radical hysterectomy alone. We would therefore agree with the recommendations of the ESTRO-ESGO consensus statement in which they recommend against routine radical hysterectomy for suspected stage II patients [11]. This would allow for avoidance of the morbidities associated with radical hysterectomy in a patient population that routinely receives adjuvant radiation [25].

There is also a lack of consensus in the use of RT which is reflected in the NCCN guidelines with lists VBT and/or EBRT as an option for those with grade 1–2 tumors and EBRT with/without VBT with/without systemic therapy [26]. Furthermore, the NCCN guidelines also state that surveillance may be appropriate for patients undergoing radical hysterectomy with negative surgical margins. In many cases, adjuvant radiation decisions are based on surgical type and uterine risk factors, extrapolating from the GOG 99, ASTEC/EN5 and PORTEC-1 trials that found lower recurrence risk with EBRT in high risk patients, though PORTEC-1 excluded patients with stage II disease [12-14]. In this cohort, approximately 68% of patients received adjuvant therapy with use of VBT or EBRT with VBT being most commonly used. We found a lower risk of death among all patients receiving radiation regardless of surgical type supporting the use of RT for all women with stage II disease.

In the current study, we noted an OS benefit for all radiation modalities including VBT alone. These findings are consistent with several recent studies. In a retrospective cohort study of patients with stage II EC, Paydar et al. [27] found that there was no difference in rate of recurrence or OS between patients receiving combination VBT and EBRT compared to VBT alone. Cannon and colleagues [28] also confirmed these findings in their retrospective study of 71 stage II patients in which they found no difference in recurrence rate between VBT and combination RT with fewer toxicities noted in the VBT alone arm. Finally, Wojcieszynski and

colleagues [29] performed a large database study using propensity-score matching in which both VBT and EBRT showed improved OS compared to observation but equivalent survival when directly comparing the 2 modalities (81% vs. 79%, NS). This suggests that VBT alone may be reasonable for selected patients.

While RT remains the treatment modality of choice for high-risk, early-stage ECs, previous studies have not found an OS benefit for chemotherapy when compared to RT (GOG 150, JGOG 2033, GICOG) [18,30,31]. This study confirms these findings with no benefit of chemotherapy alone noted. This observation remained when we stratified by histologic subtype, suggesting little benefit of chemotherapy alone in patients with stage II disease, even in those with high-risk histology. We did note a survival benefit of the combination of chemotherapy and RT with a greater magnitude of benefit than radiation alone in all histologic subtypes. These findings differ from the recently published results of GOG 249 and PORTEC 3 in which there was no survival advantage of chemotherapy and radiation when compared to radiation alone and a greater toxicity profile in the combination group [32,33]. However, only approximately 25% of each of those cohorts included patients with stage II disease, which may have diminished the ability to detect an effect of combination therapy in this particular subgroup. We do acknowledge that patients receiving combination chemotherapy and radiation made up only a small portion of the cohort. Additionally, the database lacks information regarding dosing and sequencing of therapy. Based on these results, combination therapy may be cautiously recommended for patients with stage II disease pending a detailed discussion of risks and benefits.

As this was a retrospective analysis of a large database, one of the major limitations of this study includes missing information, particularly the lack of data regarding presence of certain prognostic factors such as LVSI, which could be a serious confounder in the relationship between treatment and survival. Additionally, there is a lack of available information regarding treatment details such as radiation dosing and schedules, type of chemotherapy agents, whether patients recurred, and cause of death, which limits the conclusions we can draw from this analysis. Despite these limitations, this study includes the largest cohort of patients with FIGO 2009 stage II EC. Furthermore, while there was a small subset of patients who received a combination of radiation and chemotherapy (up to 10% of the cohort), those patients appeared to derive benefit from combination therapy. Additional strengths of this study include an assessment of the impact of surgical management and adjuvant therapy on patients with high-grade histologies.

In conclusion, women with stage II EC do not appear to benefit from routine radical hysterectomy though all patients appear to benefit from receipt of RT, regardless of modality. Additionally, there may be an added survival benefit with the combination of computed tomography and RT in patients with non-endometrioid, high-risk histologies though further studies are warranted.

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