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National patterns of care and cancer-specific outcomes of adjuvant treatment in patients with serous and clear cell endometrial carcinoma

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HIGHLIGHTS

- Brachytherapy was associated with improved cancer outcomes in stages I–II serous/clear cell endometrial cancer patients.
- Chemotherapy was associated with improved cancer outcomes in stage III patients.
- Stages I–II patients with serous histology had the best outcomes when they received both chemotherapy and brachytherapy.

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ABSTRACT

Objectives. To investigate outcomes of adjuvant therapy for serous and clear cell endometrial carcinoma, as prior studies are limited by sample size and/or patient heterogeneity. National guidelines permit substantial variations in treatment, suggesting the need for additional data.

Methods. Patients with FIGO stages I–III serous or clear cell uterine carcinoma who underwent at least total hysterectomy were identified in SEER-Medicare. Adjuvant external beam radiation, brachytherapy, and chemotherapy were determined using SEER fields and Medicare claims. The primary outcome was death from endometrial cancer (cancer-specific mortality [CSM]) evaluated using Gray's test (univariable analysis, UVA) and Fine-Gray regression (multivariable analysis, MVA).

Results. A total of 1789 patients (1437 serous, 352 clear cell) were identified. In stages I–II patients (n = 1188), brachytherapy was significant for survival in UVA ($P = 0.03$) and MVA ($P = 0.02$). Additionally, in the subset with serous histology (n = 947), chemotherapy was also significant in UVA ($P = 0.002$) and approached significance in MVA ($P = 0.05$). The 4-year CSM for stages I–II serous cancers was 25% without brachytherapy or chemotherapy, 15% with one, and 9% with both ($P \leq 0.05$ for all pairwise comparisons). In stage III patients (n = 601), chemotherapy was significant in UVA ($P = 0.002$) and MVA ($P = 0.006$). Most (81%) patients underwent lymph node dissection, which predicted lower CSM in stage III ($P = 0.001$) but not stages I–II patients.

Conclusions. Our results suggest brachytherapy benefits stages I–II serous/clear cell cancers, chemotherapy benefits stage III serous/clear cell cancers, and both chemotherapy and brachytherapy benefit stages I–II serous cancers.

1. Introduction

Endometrial cancer is the most common gynecological malignancy in the United States, with approximately 63,000 new cases and 11,000 deaths in 2018 [1]. The most common histology is endometrioid adenocarcinoma. Uterine serous carcinoma and clear cell carcinoma are high-risk histologies, accounting for 10–15% of endometrial cancer cases but a disproportionate 40–50% of endometrial cancer-related deaths [2]. Therefore, more research is needed to optimize the treatment of these less common but aggressive tumors.

While serous and clear cell cancers are included in recent clinical trials investigating adjuvant therapy of higher-risk endometrial cancers, they represent a minority of patients. For example, in PORTEC-3 and GOG-249, serous and clear cell cancers in combination comprised 20–25% of the patients enrolled. Their relatively small sample size limits the ability to draw statistically robust conclusions via subgroup analysis. Additionally, serous and clear cell cancers differ from endometrioid carcinoma, and from each other, with regard to patterns of spread and responsiveness to adjuvant therapy [3–5]. Therefore, results obtained from randomized trials consisting of mostly endometrioid carcinoma

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may not be directly extrapolated to tumors of serous or clear cell histology.

Due to these limitations, the optimal management of serous and clear cell cancers has remained unclear, and existing guidelines have relied in large part on institutional retrospective series. However, most of these series are also significantly limited in sample size (30–80 patients), and there is substantial heterogeneity with respect to inclusion of other histologies (grade 3 endometrioid and/or carcinosarcoma), patients' stages (ranging from stage I to IVA), adjuvant radiation (as some studies do not distinguish between brachytherapy and external beam radiation), and outcomes (ranging from local recurrence to overall survival). Consequently, some of these studies have reached contradictory conclusions, and national guidelines such as the National Comprehensive Cancer Network (NCCN) permit substantial variability in treatment [6].

To help address some of these uncertainties, we analyzed nationwide patterns of care and cancer outcomes of adjuvant therapy in women with serous or clear cell endometrial cancer who underwent hysterectomy. The SEER-Medicare database was selected given its large sample size, national representation of real-life practices and outcomes, cause of death information, and availability of radiation, chemotherapy, and comorbidity data.

2. Methods and materials

2.1. Data source

The Surveillance, Epidemiology, and End Results (SEER) registry records all incident cancers from 17 regional registries covering 30% of the United States population. The SEER-Medicare database links SEER cases with Medicare claims to enable identification of patients' diagnoses and procedures across time using International Classification of Diseases (ICD) and Healthcare Common Procedure Coding System (HCPCS) codes [7]. All data were de-identified. The study was approved by the Stanford University institutional review board.

2.2. Cohort identification

We queried the 2016 (most recent) release of the SEER-Medicare database for stages I–III endometrial cancers of predominantly or purely serous or clear cell histology (ICD-O-3 histology codes 8440, 8441, 8460, 8461, 8005, 8310) starting from 2004, when modern staging information became available in SEER. Stages were converted to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system based on the Collaborative Stage (CS) extension variable specifying cervical stromal invasion and CS site-specific factor 2 specifying peritoneal cytology. Patients with unknown tumor or nodal stage (TX, NX) were excluded. Also, cases that were stage IIIA solely for positive peritoneal cytology under the older FIGO staging system were excluded, as the 2009 FIGO stage could not be determined for such patients.

All patients had at least total hysterectomy according to the SEER registry (site-specific surgery codes 40-69). Cases in which radiation therapy was recorded as occurring preoperatively in SEER were excluded. To ensure adequate capture of Medicare claims and to analyze a more uniform population, patients 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. Table 1 summarizes the schema used to determine the study cohort.

2.3. Determination of study variables and outcomes

Study variables obtained directly from the SEER registry were age, race, diagnosis year, geographical SEER region, marital status, urban/rural residence, histology, stage, and lymph node dissection (determined as at least 1 lymph node examined by the pathologist). Administration of adjuvant external beam radiation, brachytherapy, and chemotherapy were identified using a combination of the SEER treatment fields and the ICD/HCPCS codes (Supplemental Table S1) recorded in patients' linked Medicare claims within 9 months of diagnosis. Comorbidity was calculated using the Charlson comorbidity index as described previously [7].

Table 1
Cohort identification algorithm.

All endometrial cancers in SEER-Medicare database since 2004	74,950
Microscopically-confirmed serous or clear cell histology	6561
Stages I–III, not TX or NX	4853
Not stage IIIA (FIGO 1988) solely for peritoneal cytology	4565
Underwent at least total hysterectomy	4278
No preoperative radiation	4237
Both part A/B and no HMO 1 year before/after diagnosis (or until death)	1890
Medicare for age only	1789

The primary study outcome was death attributable to endometrial cancer (cancer-specific mortality [CSM]). CSM was determined by the SEER cause-specific death classification and the SEER cause of death to site recode field (codes 27,020 and 27,030). Patients alive at last known follow-up were censored, and deaths not due to endometrial cancer were treated as competing risks. For the 2016 SEER-Medicare linkage, patient follow-up was through December 2014.

2.4. Statistical analysis

As there is heterogeneity of patient/tumor characteristics and cancer outcomes across stages I–III, which could affect both the selection and the efficacy of specific adjuvant interventions, we decided to analyze stages I–II and stage III separately. These stage groupings were selected based on the protocols for GOG-249 [8] and GOG-258 [9], which enrolled stages I–II serous and clear cell cancers, and outcomes of PORTEC-3 [10], which suggested a benefit of chemotherapy in stage III and not stages I–II patients.

The cumulative incidence of endometrial CSM was estimated in the presence of other-cause mortality as a competing risk. For univariable analysis, CSM was compared using Gray's test [7,11]. For multivariable analysis, the proportional hazards model of Fine and Gray was used to estimate adjusted hazard ratios for CSM. MATLAB version R2018a (MathWorks, Inc.; Natick, MA, USA) and R version 3.3.3 (R Foundation for Statistical Computing; Vienna, Austria) were used for calculations. All statistical tests were two-sided and considered significant at $P < 0.05$.

3. Results

The total study cohort consisted of 1789 patients: 1188 (66%) were stages I–II, 601 (34%) were stage III, 1437 (80%) were serous histology, and 352 (20%) were clear cell histology. Table 2 describes the patient and tumor characteristics of the cases included in this study. The median age was 74, and most patients were white and had undergone lymph node dissection. With respect to adjuvant treatment, in the stages I–II cohort, 36% received brachytherapy (BT), 51% received chemotherapy, 31% received external beam radiation (EBRT), and 32% received no adjuvant therapy; in the stage III cohort, 26% received BT, 75% received chemotherapy, 43% received EBRT, and 16% received no adjuvant therapy. By geographical region, there was no significant variation in use of EBRT ($P = 0.59$), while BT use was lower in the Midwest and South ($P < 0.0001$) and chemotherapy use was lower in the West and South ($P < 0.0001$) (Supplemental Fig. S1). Median follow-up was 3.9 years in living patients.

In the stages I–II cohort, patients treated with adjuvant BT had significantly reduced risk of death from endometrial cancer (cancer-specific mortality [CSM]) in both univariable analysis (4-year CSM 14% versus 19%, $P = 0.03$; Fig. 1) and multivariable analysis (adjusted hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.44–0.94, $P = 0.02$; Table 3). Adjuvant chemotherapy was associated with reduced CSM in

Table 2
Characteristics of the patients included in the study. SD, standard deviation; RT, radiotherapy.

	Stages I–II (n = 1188)	Stage III (n = 601)
Median age (SD)	74 (6.5)	74 (6.6)
Race		
White	936 (79%)	458 (76%)
Non-White	252 (21%)	143 (24%)
Median diagnosis year (SD)	2009 (3)	2009 (2.9)
Charlson comorbidity score		
0	714 (60%)	360 (60%)
1	186 (16%)	77 (13%)
≥2	288 (24%)	164 (27%)
Region		
Northeast	322 (27%)	146 (24%)
West	147 (12%)	65 (11%)
Midwest	170 (14%)	87 (14%)
South	549 (46%)	303 (50%)
Marital status		
Married	529 (45%)	256 (43%)
Other	659 (55%)	345 (57%)
Urban/rural residence		
Big metro	688 (58%)	347 (58%)
Metro	350 (29%)	164 (27%)
Less than metro	150 (13%)	90 (15%)
Early stage distribution		
Stage IA	733 (62%)	
Stage IB	307 (26%)	N/A
Stage II	148 (12%)	
Advanced stage distribution		
Stage IIIA–B	N/A	178 (30%)
Stage IIIC		423 (70%)
Histology		
Serous	947 (80%)	490 (82%)
Clear cell	241 (20%)	111 (18%)
Lymph node dissection		
No	254 (21%)	79 (13%)
Yes	934 (79%)	522 (87%)
Adjuvant brachytherapy		
No	756 (64%)	446 (74%)
Yes	432 (36%)	155 (26%)
Adjuvant chemotherapy		
No	585 (49%)	150 (25%)
Yes	603 (51%)	451 (75%)
Adjuvant external beam RT		
No	818 (69%)	341 (57%)
Yes	370 (31%)	260 (43%)

univariable analysis ($P = 0.01$; Supplemental Fig. S2), but was not significant in multivariable analysis ($P = 0.11$; Table 3). EBRT was not significant (Supplemental Fig. S3, Table 3).

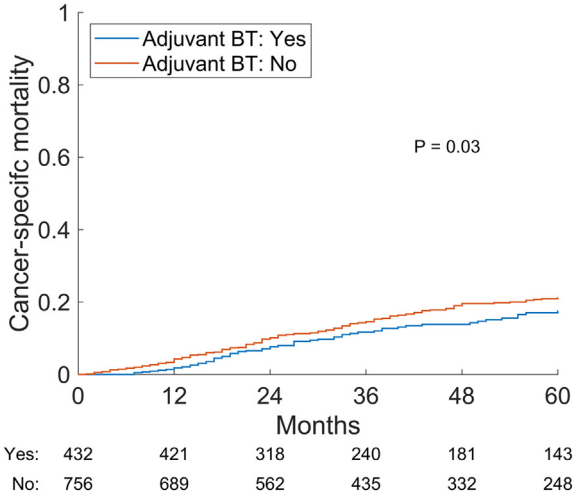

Fig. 1. Cancer-specific mortality (CSM) for stages I–II serous and clear cell cancers according to receipt of adjuvant brachytherapy (BT).

Table 3
Fine-Gray multivariable modeling of predictors for cancer-specific mortality. HR, hazard ratio.

	Stages I–II		Stage III	
	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Age	1.01 (0.99–1.04) per year	0.23	1.00 (0.98–1.02) per year	0.78
Race				
White	1	–	1	–
Non-White	1.74 (1.27–2.39)	**0.0006**	0.84 (0.62–1.12)	0.23
Diagnosis year	0.94 (0.89–0.99) per year	**0.03**	0.94 (0.90–0.99) per year	**0.01**
Charlson comorbidity score				
0	1	–	1	–
1	1.23 (0.86–1.77)	0.26	1.20 (0.80–1.81)	0.38
≥2	0.91 (0.65–1.28)	0.59	1.13 (0.86–1.49)	0.37
Region				
Northeast	1	–	1	–
West	1.08 (0.66–1.76)	0.76	0.89 (0.56–1.42)	0.63
Midwest	1.11 (0.71–1.74)	0.65	1.18 (0.81–1.70)	0.39
South	1.00 (0.68–1.46)	0.99	0.95 (0.70–1.28)	0.73
Marital status				
Married	1	–	1	–
Other	0.84 (0.64–1.12)	0.23	1.07 (0.83–1.38)	0.58
Urban/rural residence				
Big metro	1	–	1	–
Metro	1.09 (0.79–1.49)	0.61	1.24 (0.95–1.63)	0.12
Less than metro	1.26 (0.82–1.92)	0.29	0.83 (0.57–1.20)	0.32
Early stage distribution				
Stage IA	1	–	N/A	
Stage IB	2.31 (1.69–3.16)	<**0.0001**		
Stage II	3.00 (2.03–4.44)	<**0.0001**		
Advanced stage distribution				
Stage IIIA–B	N/A		1	–
Stage IIIC			2.06 (1.32–3.24)	**0.002**
Histology				
Serous	1	–	1	–
Clear cell	0.97 (0.67–1.39)	0.85	0.80 (0.57–1.12)	0.19
Lymph node dissection				
No	1	–	1	–
Yes	0.96 (0.69–1.33)	0.81	0.39 (0.22–0.69)	**0.001**
Adjuvant brachytherapy				
No	1	–	1	–
Yes	0.64 (0.44–0.94)	**0.02**	0.84 (0.63–1.12)	0.24
Adjuvant chemotherapy				
No	1	–	1	–
Yes	0.77 (0.56–1.06)	0.11	0.66 (0.50–0.89)	**0.006**
Adjuvant external beam RT				
No	1	–	1	–
Yes	1.29 (0.91–1.84)	0.15	0.99 (0.76–1.28)	0.94

Bold values indicates statistically significance at < 0.05.

Since chemotherapy was significant in univariable but not multivariable analysis, and prior reports have indicated that serous cancer is more chemo-responsive than clear cell [12], we performed a sensitivity analysis in the stages I–II serous subgroup (n = 947). Chemotherapy was more significant in univariable analysis of CSM ($P = 0.002$) and approached significance in multivariable analysis (adjusted HR 0.71; 95% CI 0.50–1.00, $P = 0.05$), while BT remained significant (univariable and multivariable $P = 0.004$) and EBRT remained non-significant. Accordingly, the risk of death from endometrial cancer for stages I–II serous patients was highest without BT or chemotherapy (n = 338; 36% of patients), intermediate with one but not both (n = 365; 38% of patients), and lowest with the combination of BT and chemotherapy (n = 244; 26% of patients), with 4-year CSM of 25% versus 15% versus 9% respectively ($P \leq 0.05$ for all pairwise comparisons; Fig. 2).

In the stage III cohort, patients treated with chemotherapy had significantly reduced risk of death from endometrial cancer in both univariable analysis (4-year CSM 45% versus 55%, $P = 0.002$; Fig. 3) and multivariable analysis (adjusted HR 0.66; 95% CI 0.50–0.89, $P = 0.006$; Table 3). BT and EBRT were not significant (Supplemental Figs. S4–5, Table 3). Since clear cell carcinoma is reportedly more

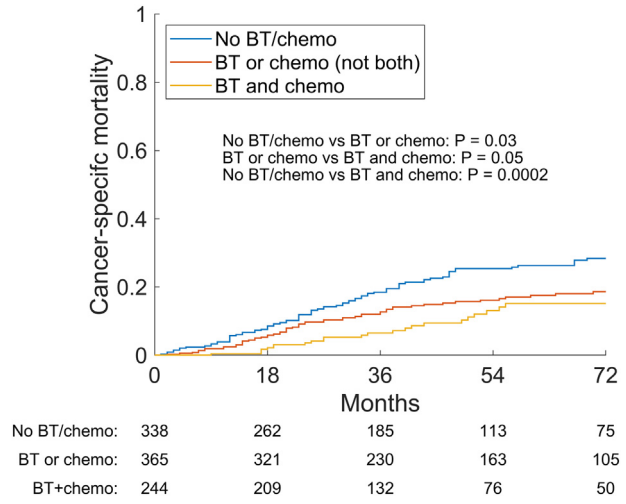

Fig. 2. Cancer-specific mortality (CSM) for stages I–II cancers of serous histology in patients who received neither brachytherapy (BT) or chemotherapy, BT or chemotherapy (not both), or both.

refractory to chemotherapy, we performed a sensitivity analysis in the stage III clear cell subgroup. Even though this was a small subset of patients (n = 111), chemotherapy remained significant in univariable and multivariable analysis ($P = 0.03$ and 0.003, respectively), and EBRT was nearly significant in multivariable analysis (adjusted HR 0.51; 95% CI 0.24–1.04, $P = 0.07$).

Besides adjuvant therapy, other patient and tumor predictors of endometrial cancer-specific mortality are listed in Table 3. Within both the stages I–II and stage III cohorts, increasing FIGO stage was associated with greater CSM, and more recent year of diagnosis was associated with decreased CSM. Non-white race predicted increased CSM in stages I–II patients ($P = 0.0006$) but not stage III. Conversely, undergoing lymph node dissection (median nodes removed: 15 for stages I–II, 14 for stage III) predicted decreased CSM in stage III patients ($P = 0.001$) but not stages I–II.

4. Discussion

This work is a large-scale, national study of cancer-specific outcomes of adjuvant BT, EBRT, and chemotherapy in patients with serous or clear cell endometrial carcinoma. A strength of our study is the primary outcome of death from endometrial cancer. In retrospective studies, healthier patients may be more likely to tolerate and receive adjuvant treatment, which confounds overall survival. Thus, we analyzed death from endometrial cancer, and adjusted for comorbidity in the multivariable analysis, to reduce selection bias. This analysis was only possible using the linked SEER-Medicare database, as it uniquely incorporates data on radiation, chemotherapy, comorbidity, and cause of death. In contrast, the SEER-only database lacks chemotherapy and comorbidity data, and the National Cancer Database (NCDB) lacks cause of death data, precluding the analysis of cancer-specific outcomes. Additionally, our study used a competing risks analysis, which is appropriate as most endometrial cancer patients are elderly and may die from other causes.

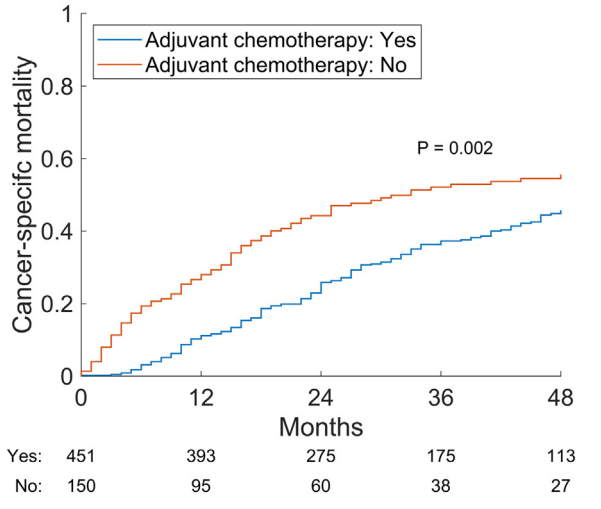

Fig. 3. Cancer-specific mortality (CSM) for stage III serous and clear cell cancers according to receipt of adjuvant chemotherapy.

Our findings add significantly to the existing literature, as prior studies have been limited by small sample size and/or heterogeneity of patient characteristics. In the stages I–II cohort, BT was the only treatment to significantly improve cancer-specific outcomes in both univariable and multivariable analysis. No modern trials have investigated BT for serous/clear cell cancers in a randomized fashion, as they were excluded from PORTEC-2. Our study is consistent with institutional studies that have found excellent local control and disease-free survival in early-stage serous and clear cell patients treated with adjuvant BT, with or without chemotherapy [13–15]. In a series of 79 stages I–II patients, adjuvant radiation (BT and/or EBRT) was associated with improved relapse-free and disease-specific survival [16]. Even for stage IA serous cancer, BT has been found to significantly decrease vaginal recurrence (2.6% versus 10.9%) [17]. Yet despite these data, in the NCCN guidelines, BT is optional [6].

Additionally, chemotherapy was also highly significant in the stages I–II serous subgroup in univariable analysis, and approached significance in multivariable analysis. Such patients had the best survival outcomes with both BT and chemotherapy, while EBRT was not significant. These results are consistent with previous studies that showed serous cancers are relatively chemo-sensitive and have a predilection for extrapelvic relapse [12]. Even stage IA serous cancers with complete surgical staging have up to 20–30% recurrence rate, which appears to be reduced by chemotherapy (9% vs 26%, $P = 0.03$) [12]. Accordingly, several institutional studies have shown that chemotherapy is associated with improved progression-free and cancer-specific survival [18–20]. Adjuvant chemotherapy and radiation were both found to be beneficial in some series [21,22], while others have found a benefit to chemotherapy and not radiation [23,24], although radiation in these studies was an aggregate of EBRT and BT.

Recently, a large multi-institutional retrospective series of 414 patients with stage IA serous or clear cell cancer reported a 5-year disease-free survival benefit for adjuvant BT (96% versus 84%, $P = 0.007$) and chemotherapy (84% versus 69%, $P = 0.009$); by contrast, pelvic EBRT was not significant in univariable or multivariable analysis, corroborating our results [25]. Similarly, another study of 84 stage I serous/clear cell patients treated with BT and chemotherapy found no added benefit of EBRT [26].

Interestingly, these data and our findings differ from the preliminary results of GOG-249, which included higher-risk stage I endometrioid, stage II endometrioid, and stages I–II serous/clear cell cancers. Patients were randomized to receive adjuvant pelvic EBRT alone (permitting BT boost for stage II patients and any patients with serous or clear cell histology) versus combination BT/chemotherapy [8]. Recurrence-free and overall survival were similar between the two arms, while the EBRT arm had decreased pelvic/para-aortic failures, no difference in vaginal or distant failure, and less acute toxicity, implying that EBRT alone should remain standard of care [8]. However, as serous/clear cell cancers comprised only 20% of the patients in GOG-249, and the full trial is not yet published, caution is required when applying these results to patients with serous or clear cell histology. An ongoing European phase II randomized trial (ENGOT-EN2-DGCG) is comparing postoperative observation versus chemotherapy for stages I–II intermediate/high-risk endometrial cancer (including serous/clear

cell), with vaginal BT allowed in both arms [27]. Results from this trial will provide crucial evidence regarding the efficacy of chemotherapy for higher-risk, early-stage patients.

In the stage III cohort, chemotherapy was the only treatment to be significant in both univariable and multivariable analysis. This is consistent with results from PORTEC-3, which included higher-risk stage I endometrioid, stages II–III endometrioid, and stage I-III serous/clear cell cancers [10]. Patients were randomized to receive pelvic EBRT alone versus chemoradiation with pelvic EBRT followed by additional chemotherapy. Failure-free survival was significantly improved by the addition of chemotherapy in stage III patients, but not in stages I–II on subgroup analysis. Additionally, the PORTEC-3 subgroup analysis of non-endometrioid histology (serous/clear cell/other) showed a benefit to chemotherapy (5-year failure-free survival 69% versus 59%; HR 0.60, $P = 0.036$), although the subgroup analysis of serous cancers alone was not significant due to limited sample size (HR 0.63, $P = 0.11$) Previous retrospective studies have also found a benefit of chemotherapy in advanced-stage serous and clear cell patients, with or without radiation [28,29].

We also found that EBRT was not significant in stage III patients, which is consistent with preliminary results from GOG-258 that included stages III–IVA (endometrioid, serous, clear cell) and stages I–II serous/clear cell cancers with positive peritoneal cytology [9,30]. Patients were randomized to chemotherapy alone versus chemoradiation with pelvic EBRT followed by additional chemotherapy. The addition of EBRT did not affect relapse-free survival, although it did reduce rates of vaginal, pelvic, and para-aortic recurrences. Interestingly, we found that EBRT was nearly significant for stage III clear cell cancers ($P = 0.07$) on subgroup analysis, despite the small size of this subgroup (111 patients). Clear cell cancers are more refractory to chemotherapy than serous histology, and indeed, prior studies have also suggested a greater benefit to EBRT for clear cell carcinoma [12,31].

Similarly, GOG 122 showed that progression-free and overall survival were superior for chemotherapy (doxorubicin/cisplatin) compared to EBRT (whole abdominal irradiation with pelvic boost) for stages III–IV endometrial carcinoma [32]. Interestingly, there was no difference between chemotherapy and EBRT in the serous subgroup in GOG 122, while we found that chemotherapy benefited stage III serous/clear cell patients and EBRT did not. However, serous cancers comprised only 20% of patients in GOG 122, thus limiting the statistical power in that subgroup. Additionally, carboplatin/paclitaxel has largely become the preferred chemotherapy regimen for adjuvant treatment of uterine cancer and may be more efficacious and less toxic than the regimen of doxorubicin/cisplatin used in GOG 122, which may also explain why we found a significant cancer specific survival benefit to chemotherapy for stage III serous/clear cell cancers.

In addition to adjuvant treatment, FIGO stage, year of diagnosis, race, and lymph node dissection were significant predictors of death from endometrial cancer. The HR of 0.94 for year of diagnosis indicates that for every year since 2004 (the starting year of patients included in the study), the hazard of CSM decreased by 6%. This may be due to improved imaging/workup over time (with consequent stage migration), improvements to supportive care (patients able to tolerate and complete more therapy), and better salvage/systemic therapies (including chemotherapy regimens) in later years. Non-white race as an adverse feature may reflect socioeconomic barriers to care (including workup/staging and ability to complete the full prescribed course of therapy) [33], as well as biological factors, such as increased HER2/neu expression in black women with serous carcinoma [34] and differences in estrogen metabolism [33]. Interestingly, this racial disparity did not extend to stage III patients, who have significantly worse outcomes overall, possibly indicating that the advanced stage supersedes the contribution of socioeconomic and racial factors. Undergoing lymph node dissection predicted significantly lower CSM for stage III (but not stage I-II) patients. In the absence of gross nodal metastases, stage III patients are more likely to have occult nodal disease, and thus are more likely to benefit from lymph node dissection. The database does not distinguish between sentinel lymph node biopsy versus complete lymph node dissection.

The primary limitation of our study is its retrospective nature. We used competing risks analysis and multivariable modeling to adjust for potential confounders, but residual selection bias is possible. Thus, our findings remain primarily hypothesis-generating and must be evaluated in the context of randomized evidence, when available. As it is a large national registry, there are potential limitations regarding accuracy of data input to SEER, although the database includes numerous quality control checks [35] and our combined use of the SEER treatment fields and Medicare claims reduces under-ascertainment of adjuvant therapy [36]. The database also does not contain data regarding RT details (fields, dose, fractionation), sites of recurrence, or lymphovascular invasion (LVSI). However, traditional risk factors for endometrial cancer recurrence may not be applicable to high-risk histologies [24], and LVSI was also not prognostic of failure-free or overall survival in PORTEC-3 [10]. Our study did not include modern (FIGO 2009) stages I–II serous patients with positive peritoneal cytology, since their stage could not be converted from FIGO 1988 accurately. However, such patients are still likely to benefit from at least adjuvant chemotherapy, since we found that chemotherapy benefited serous patients in both the stages I–II and stage III cohorts. Mode of surgery (laparoscopic or open) is not provided in the SEER site-specific surgery code; however, a previous prospective randomized study (GOG LAP2 trial) suggested similar outcomes between laparoscopy and laparotomy for at least stages I–II uterine cancer [37]. Finally, our results are based on a Medicare-aged population and may not be applicable to younger patients, although younger women would have fewer competing risks for mortality and stand to gain even more from adjuvant treatment.

In summary, BT was associated with significantly improved cancer outcomes in stages I–II serous/clear cell carcinoma patients, and both chemotherapy and BT appeared to benefit early-stage patients with serous histology. In stage III patients, chemotherapy was associated with improved cancer outcomes; EBRT may also benefit stage III patients with clear cell histology. As existing studies (both clinical trials and retrospective series) are limited by sample size and patient heterogeneity, our study provides additional insight into the optimal adjuvant management of serous and clear cell cancers. More research, ideally in a randomized setting, is warranted to confirm these results and improve the outcomes for these aggressive tumors.

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Disclosures/conflicts of interest

The authors declare no competing financial interests.

Author contributions

M.X.: conceptualization, data curation, formal analysis, investigation, methodology, writing (original draft, review and editing). D.P.E.: investigation, methodology, writing (review and editing). E.A.K.: conceptualization, investigation, methodology, project administration, supervision, writing (review and editing).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.12.007.

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