Original Article

Is there different prognosis between cervical endometrioid adenocarcinoma and ordinary cervical adenocarcinoma in a propensity score matching study based on the surveillance, epidemiology, and end results (SEER) database?

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Background: There has been lack of guidance for stratify treatment between cervical endometrioid adenocarcinoma (EC) and ordinary cervical adenocarcinoma (AC), therefore understanding the difference of prognosis between EC and AC is important for individualized therapy for these patients.

Methods: In this study, we compare the survival outcomes between cervical EC and AC patients from the SEER database. we analyzed 2,554 patients for overall survival (OS) and 2,527 patients for disease-specific survival (DSS), Cox regression and Kaplan-Meier analyses were conducted to analyze the survival outcomes of the AC and EC patients, a 1:1 propensity score matching (PSM) method was used to match patients and balance various factors, OS and DSS were analyzed among the subgroups before and after 1:1 PSM.

Results: In the unmatched cohort, in the multivariate analysis, no statistically significant difference was found in terms of OS (P=0.24) and DSS (P=0.20) between the EC and AC patients, The 3- and 5-year OS rates were 77.89% and 72.65% for the AC patients, and 83.38% and 75.64% for the EC patients respectively. The 3- and 5-year DSS rates were 84.93% and 79.69% for the EC patients, 83.97% and 76.78% for the AC patients, respectively. In the PSM cohort, 280 AC patients and 280 EC patients were included in the analysis of OS. 273 AC patients and 275 EC patients were included in the analysis of DSS, the Kaplan-Meier analysis and the multivariate analysis also produced similar results for the unmatched groups.

Conclusions: There were no statistically significant differences in OS and DSS between the cervical EC and AC patients.

Keywords: Cervical endometrioid adenocarcinoma (EC); ordinary cervical adenocarcinoma (AC); survival; propensity score matching (PSM)

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Introduction

Cervical cancer is the most common female genital tract malignancy tumor worldwide (1). Over the last decade, the incidence and mortality rates of cervical cancer have been decreasing (2); however, it remains a serious public health problem. In 2020, approximately 604,127 new cases of cervical cancer were diagnosed and 341,831 patients died of the disease worldwide (3). Cervical cancer has many histological subtypes, of which the 2 most common are squamous cell carcinoma (SCC) and adenocarcinoma. In recent years, with the increased detection of the premalignant disease, wider cytological screening, and the human papillomavirus (HPV) vaccination, the incidence rate of SCC has decreased (4). However, the cervical adenocarcinoma rate has continued to increase each year in Europe, particularly among reproductive age women (5,6). As adenocarcinoma currently comprises about 20% of all cervical cancers (7), we should be concerned about the prognosis of cervical adenocarcinoma, and personalized treatments for the different subgroups are needed.

Cervical adenocarcinoma is the 2nd most common histological subtype of cervical cancer, and can be subdivided into many pathological subtypes. Different subtypes have different clinical behaviors, different biological signatures, different treatment outcomes, and different prognoses (8-11). However, recent cervical cancer guidelines recommend the same treatment for both SCC and adenocarcinoma. Research on the efficacy of the treatment for the different subtypes is insufficient. In relation to the cervical adenocarcinoma histological subtypes, the most common subtype of cervical cancer is ordinary adenocarcinoma, but another subtype is cervical endometrioid adenocarcinoma (EC). EC is a rare histological subtype of adenocarcinoma in the uterine cervix, and accounts for only 1.1% of all cervical adenocarcinomas (12), EC originates in the cervix and exhibits endometrioid morphological features but is not associated with high-risk HPV infection. At present, there is no difference in the treatment administered to ordinary cervical adenocarcinoma (AC) and EC patients. Additionally, there is a lack of specific level 1 evidence to guide patient management. However, the same treatment may not be appropriate for AC and EC patients. Comparisons of the prognostic differences between cervical EC and AC patients have important significance in determining individualized treatment plans.

Previous study has shown that the epidemiology, prognostic factors, and treatment response of cervical adenocarcinoma patients differ to those of SCC patients (13). Many researchers have sought to study whether different histological subtypes of cervical cancer have any effect on survival; however, the results of these studies have differed (6,14). Few studies have examined the difference between EC and AC. Only Yoshida *et al.* reported the study on endocervical type and endometrioid type cervical adenocarcinoma of Seventy-seven patients with cervical adenocarcinoma were treated at the Department of Obstetrics and Gynecology, Okayama University Medical School from 1974 to 1987 and no significant differences were found between endocervical type and endometrioid type in the 5-year survival rate (15). Thus, studying a large population-based sample and using real-world data from multiple high-quality population-based cancer registries might generate more detailed and accurate results.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) in the United States (US) is a high-quality database containing information from multiple institutions, which collects cancer survival data from population-based cancer registries covering about 34.6% of the US population (16). The purpose of our study was to further accurate assess survival result differences by comparing the overall survival (OS) and disease-specific survival (DSS) of patients with pathologically diagnosed AC and EC based on data from the SEER database, In order to control the influence of confounding factors, we use a propensity score matching (PSM) analysis. In clinical sense, EC may be associated with better survival than AC. Our findings have important implications for enabling better individualized personalized treatment for these patients. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1180/rc).

Methods

Patients and data collection

Patients from the Surveillance, Epidemiology, and End Results (SEER) Program [2010–2015] were enrolled in this study. SEER is a population-based cancer registry database (16). The database is a public source of information that provides data on the incidence, mortality, prevalence, lifetime risk statistics, and survival of cancer patients in the US (17). We used SEER*Stat software (version 8.3.8;

Surveillance Research Program, NCI, Bethesda, MD) to access the information in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was not required, as the retrospective data were identified from the SEER database. However, obtaining the SEER Research Data File required a data use-agreement submission. The patient data in this study were anonymously managed at all stages.

We identified and extracted the data of 95,234 cervical adenocarcinoma patients from the SEER database from January 2010 to January 2015 for the initial analysis. OS was the outcome variable.

To be eligible for inclusion in the analysis, patients had to meet the following inclusion criteria: (I) have a primary diagnosis of cervical AC from 2010 to 2015; (II) have a follow-up time ≥1 month; (III) have complete clinicopathological information (including information about the number of lymph nodes examined and the surgical situation) and complete Federation International of Gynecology and Obstetrics (FIGO) Clinical Staging (version 2009) information; (IV) have been pathologically diagnosed with cervical AC; (V) have data available on the ICD-0-3 histology codes of the histological subtypes, which were grouped as EC (8140/3) or AC (8380/3).

Patients were excluded from the study if they met any of the following exclusion criteria: (I) had been followed-up <1 month; (II) did not have cervical AC as the first or only primary malignant tumor; and/or (III) had incomplete clinicopathological information (including information about the number of lymph nodes examined and the surgical situation) or incomplete FIGO Clinical Staging (version 2009) information.

It should be noted that we collected data from 2010 to 2015 because the FIGO Clinical Staging (version 2009) system was renewed in 2018. DSS was the outcome variable. A total of 2,527 patients were eligible for inclusion in the final data analysis, and 92,707 patients were excluded based on the predefined exclusion criteria. Additionally, patients who were unknown information about DSS were excluded from our target population.

Clinical covariates

The following data about each patient were obtained from the SEER database: race, age at diagnosis, FIGO clinical stage, primary site, marital status, number of regional lymph nodes, number of regional metastasis lymph nodes, surgery, radiation, and chemotherapy.

Patients were allocated to the following four groups based on age at diagnosis: (I) 21–39 years old; (II) 40–44 years old; (III) 45–59 years old; and (IV) 60–97 years old. Using the survMisc package in R, the optimal cutoff value of the number of regional lymph nodes was determined to be 18. Patients were allocated to the following three groups based on the number of regional lymph nodes: (I) 0; (II) 0–18; and (III) 19–90. Using the survMisc package in R, the optimal cutoff value of the number of regional positive lymph nodes was determined to be 2. Patients were allocated to the following three groups based on the number of regional positive lymph nodes: (I) 0; (II) 0–2; and (III) 3–23. Patients were allocated to the following three groups based on marital status: (I) single/unmarried; (II) married; and (III) divorced/other. Patients were allocated to the following two groups based on primary site: (I) C53.0 (neck of the uterus); and (II) other. Patients were allocated to the following two groups based on FIGO Clinical staging: (I) IA1–IIA2; and (II) IIB–IVB.

Assessment of prognosis

OS and DSS were the primary outcome of this study. OS was defined as the time from the period of diagnosis to the last follow-up or death. DSS was defined as the time from diagnosis to death from cervical AC. The last follow-up date was December 31, 2015.

PSM is a statistical method that uses non-experimental or observational data for intervention effect analyses. In this study, the baseline data, including data on radiotherapy, chemotherapy, staging, and age, were uneven between the EC and AC groups, which could have caused the results to be biased. Thus, a 1:1 PSM method was used to match patients and balance various factors (18). The variables used for matching were race, age at diagnosis, FIGO clinical staging, primary site, marital status, number of regional lymph nodes, number of regional metastasis lymph nodes, surgery, radiation, and chemotherapy. The nearest neighbor matching algorithm without replacement was applied to ensure adequate matches, the loveplot to test equilibrium before and after PSM.

Statistical analysis

We compared the demographic, clinical, and treatment characteristics of EC and AC patients using the χ^2 test. The Kaplan-Meier method was used to examine the cumulative survival curves. The log-rank test was used to compare

these curves. The Cox proportional-hazard model was used in the univariate and multivariate survival analyses, and hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated. We conducted subgroup analyses to determine the HRs of the EC and AC patients in the matched population stratified according to the covariates. The statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA) and R software (version 4.0.5, http://www.R-project.org).

Results

Clinical and demographic characteristics of the study cohort

In total, on the basis of the inclusion and exclusion criteria, 95,234 patients with cervical cancer were eligible for inclusion in this study. Of these, when OS was the outcome variable, 2,554 patients were eligible for inclusion in the final data analysis, and 92,680 patients were excluded based on the predefined exclusion criteria. The demographic, clinical, and treatment characteristics of these selected patients before and after PSM are set out in *Table 1*. Of the 2,554 patients, 2,274 (89.04%) had AC and 280 (10.96%) had cervical endometriosis adenocarcinoma (EC). Compared to the AC patients, a higher percentage of EC patients underwent surgery. When DSS was the outcome variable, 2,527 patients were eligible for inclusion in the final data analysis, and 92,707 patients were excluded based on the predefined exclusion criteria. The demographic, clinical, and treatment characteristics of the included patients before and after PSM are set out in *Table 2*.

Survival analysis of the unmatched patients

A survival analysis was performed using the Kaplan-Meier method to estimate the OS and DSS of the unmatched patients (see *Figure 1A,1B*). The 3- and 5-year OS rates were 77.89% and 72.65% for the AC patients, and 83.38% and 75.64% for the EC patients, respectively. The Kaplan-Meier analysis revealed no significant difference in the OS of the EC and AC patients (P=0.1; see *Figure 1A*). The 3- and 5-year DSS rates were 79.70% and 75.54% for the AC patients, 84.93% and 79.69% for the EC patients, respectively. The EC patients had a significantly better prognosis of DSS than the AC patients (P=0.047; see *Figure 1B*). The survival package in the R was used to analyze the Kaplan-Meier above.

Each variable satisfied the proportional hazards (Ph) test (see Figure S1A,S1B). The results of the univariate and multivariate analyses of potential predictors of OS are set out in Table S1 and Figure S2. In the univariate analysis, the variables of race, FIGO stage, primary site, chemotherapy, regional nodes, positive nodes, marital status, surgery, and age group were identified as significant predictive factors of OS. In the multivariate analysis, all the variables retained independent significance for OS, except for the primary site, marital status, and tumor type. In the univariate analysis, the AC patients had a poorer prognosis in terms of OS than the EC patients (P=0.1). Similar results were found after adjustment in the multivariate analysis. No significant differences were observed in terms of tumor type (i.e., EC *vs.* AC). The results of the univariate and multivariate analyses of the potential predictors of DSS are set out in Table S2. In the univariate analysis, the factors affecting DSS were tumor type (EC *vs.* AC), race, FIGO stage, primary site, chemotherapy, regional nodes, lymph node metastasis, marital status, surgery history, and age group. In the multivariate analysis, the results of the AC and EC patients were similar in terms of OS. In the univariate analysis, the AC patients had a worse DSS prognosis than the EC patients (P=0.047). After adjustment in the multivariate analysis, no significant differences were observed in terms of tumor type (i.e., EC *vs.* AC).

Based on the above-mentioned results, we performed subgroup analyses and interaction tests to further assess the differences in OS between the EC and AC patients as stratified by patient characteristics (see *Figure 2*). In the single/unmarried subgroup, the EC patients were predicted to have a better prognosis than the AC patients (HR =0.477; 95% CI: 0.246–0.927; P=0.029). However, in the divorced/unknown subgroup, the EC patients were predicted to have a poorer prognosis than the AC patients, but no significant differences were observed. The interaction tests revealed that there were significant differences in the different race subgroups, the different marital subgroups, and the different age subgroups. Thus, race, age, and marital status may be effect modifiers of the OS of EC and AC patients. No significant differences were observed in relation to the other variables. The same subgroup analyses and interaction tests were conducted for DSS (see *Figure 3*), and the analyses produced similar results.

Survival analysis of the matched groups

In this study, we used the 1:1 PSM method to match the

Table 1 The characteristics of the cervical EC and AC patients before and after PSM when OS was the outcome variable

Characteristics	PSM_before			PSM_after		
	AC (n=2,274)	EC (n=280)	P value	AC (n=280)	EC (n=280)	P value
Age, median [Q1, Q3]	46 [38, 58]	50 [42, 60.25]	<0.001	50 [41, 61]	50 [42, 60.25]	0.836
Race, n [%]			0.842			0.804
Black	179 [8]	23 [8]		20 [7]	23 [8]	
Other	287 [13]	32 [11]		29 [10]	32 [11]	
White	1,808 [80]	225 [80]		231 [82]	225 [80]	
Primary site [%]			0.115			0.932
Cervix uteri	1,125 [49]	124 [44]		122 [44]	124 [44]	
Other	1,149 [51]	156 [56]		158 [56]	156 [56]	
Surgery [%]			0.001			0.615
No	713 [31]	61 [22]		67 [24]	61 [22]	
Yes	1,561 [69]	219 [78]		213 [76]	219 [78]	
Radiation [%]			<0.001			0.862
No	1,802 [79]	175 [62]		172 [61]	175 [62]	
Yes	472 [21]	105 [38]		108 [39]	105 [38]	
Chemotherapy [%]			0.201			0.671
No	1,354 [60]	155 [55]		149 [53]	155 [55]	
Yes	920 [40]	125 [45]		131 [47]	125 [45]	
Marital [%]			0.584			0.902
Divorced/unknown	510 [22]	58 [21]		57 [20]	58 [21]	
Married	1,152 [51]	151 [54]		156 [56]	151 [54]	
Single/unmarried	612 [27]	71 [25]		67 [24]	71 [25]	
Regional nodes [%]			<0.001			0.492
0	1,119 [49]	95 [34]		99 [35]	95 [34]	
0–18	648 [28]	111 [40]		119 [42]	111 [40]	
19–90	507 [22]	74 [26]		62 [22]	74 [26]	
Positive nodes [%]			<0.001			0.977
0	2,131 [94]	244 [87]		243 [87]	244 [87]	
0–2	93 [4]	25 [9]		25 [9]	25 [9]	
3–23	50 [2]	11 [4]		12 [4]	11 [4]	
FIGO [%]			0.952			0.861
IA1–IIA2	1,445 [64]	179 [64]		176 [63]	179 [64]	
IIB–IVB	829 [36]	101 [36]		104 [37]	101 [36]	
Age category [%]			<0.001			0.885
21–39	663 [29]	52 [19]		55 [20]	52 [19]	
40–44	376 [17]	40 [14]		34 [12]	40 [14]	
45–59	703 [31]	107 [38]		111 [40]	107 [38]	
60–97	532 [23]	81 [29]		80 [29]	81 [29]	

AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; PSM, propensity score matching; OS, overall survival; FIGO, Federation International of Gynecology and Obstetrics.

Table 2 The characteristics of the cervical EC and AC patients before and after PSM when DSS was the outcome variable

Variables	PSM_before			PSM_after		
	AC (n=2,252)	EC (n=275)	P	AC (n=273)	EC (n=275)	P
Age, median [Q1, Q3]	46 [38, 57]	50 [41.5, 60]	<0.001	50 [42, 60]	50 [41.5, 60]	0.391
Race [%]			0.722			0.615
Black	178 [8]	23 [8]		23 [8]	23 [8]	
Other	283 [13]	30 [11]		23 [8]	30 [11]	
White	1,791 [80]	222 [81]		227 [83]	222 [81]	
Primary site [%]			0.136			0.349
Cervix uteri	1,111 [49]	122 [44]		133 [49]	122 [44]	
Other	1,141 [51]	153 [56]		140 [51]	153 [56]	
Surgery [%]			0.002			0.724
No	704 [31]	60 [22]		64 [23]	60 [22]	
Yes	1,548 [69]	215 [78]		209 [77]	215 [78]	
Radiation [%]			<0.001			0.704
No	1,784 [79]	173 [63]		177 [65]	173 [63]	
Yes	468 [21]	102 [37]		96 [35]	102 [37]	
Chemotherapy [%]			0.227			1
No	1,343 [60]	153 [56]		151 [55]	153 [56]	
Yes	909 [40]	122 [44]		122 [45]	122 [44]	
Marital [%]			0.652			0.449
Divorced/unknown	503 [22]	57 [21]		69 [25]	57 [21]	
Married	1,138 [51]	147 [53]		137 [50]	147 [53]	
Single/unmarried	611 [27]	71 [26]		67 [25]	71 [26]	
Regional nodes [%]			<0.001			0.908
0	1,103 [49]	94 [34]		95 [35]	94 [34]	
0–18	645 [29]	108 [39]		110 [40]	108 [39]	
19–90	504 [22]	73 [27]		68 [25]	73 [27]	
Positive nodes [%]			0.001			0.605
0	2,110 [94]	241 [88]		243 [89]	241 [88]	
0–3	111 [5]	28 [10]		22 [8]	28 [10]	
4–23	31 [1]	6 [2]		8 [3]	6 [2]	
FIGO [%]			0.875			0.633
IA1–IIA2	1,434 [64]	177 [64]		182 [67]	177 [64]	
IIB–IVB	818 [36]	98 [36]		91 [33]	98 [36]	
Age category [%]			<0.001			0.841
21–39	662 [29]	52 [19]		50 [18]	52 [19]	
40–44	375 [17]	40 [15]		33 [12]	40 [15]	
45–59	697 [31]	107 [39]		111 [41]	107 [39]	
60–97	518 [23]	76 [28]		79 [29]	76 [28]	

AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; PSM, propensity score matching; DSS, disease-specific survival; FIGO, Federation International of Gynecology and Obstetrics.

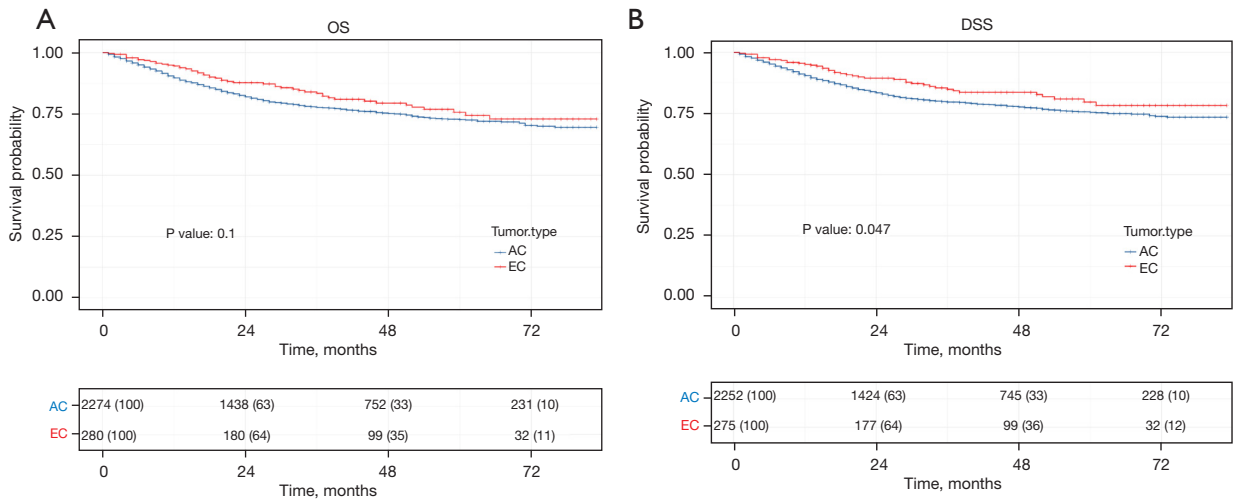

Figure 1 Kaplan-Meier plot and log-rank tests of OS (A) and DSS (B) in the unmatched cohort. AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; OS, overall survival; DSS, disease-specific survival.

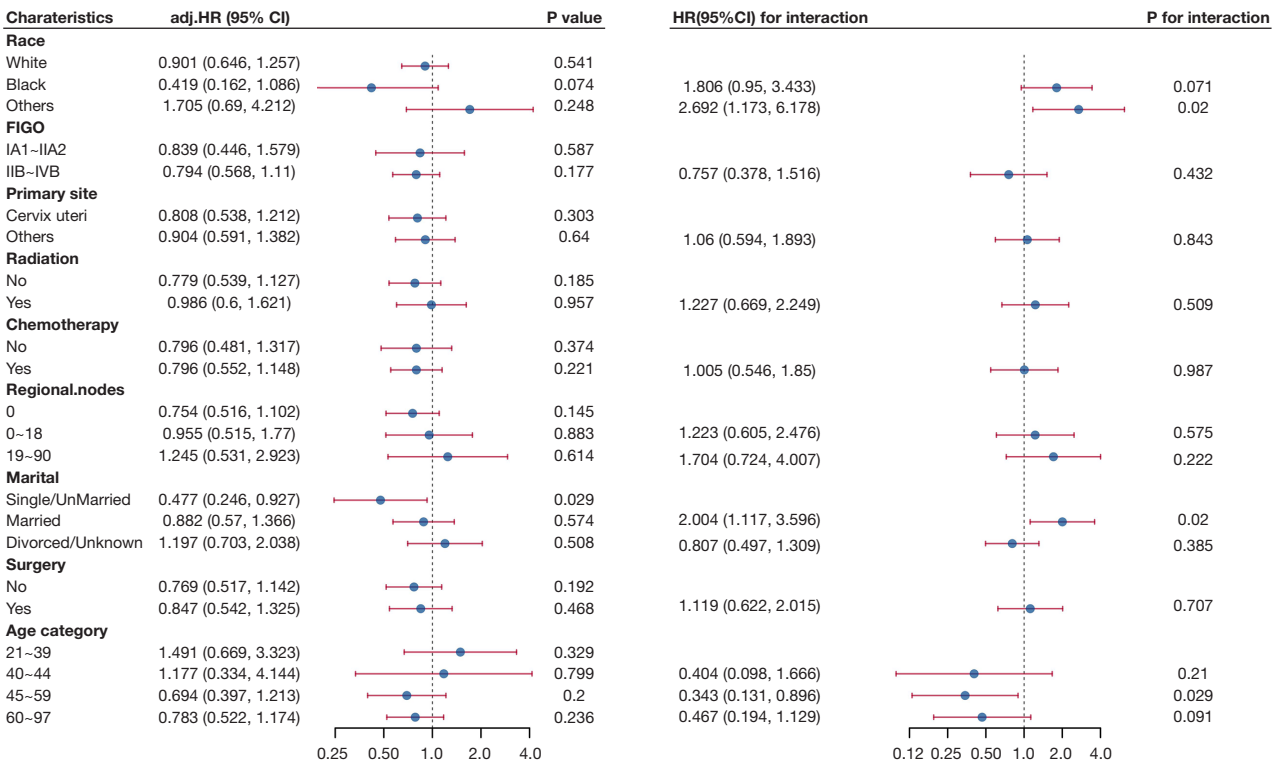

Figure 2 Forest plot of the HRs of the EC patients compared to the AC patients in the subgroup analysis of OS in the unmatched cohort. EC, cervical endometrioid adenocarcinoma; AC, ordinary cervical adenocarcinoma; OS, overall survival; adj.HR, adjusted HR; FIGO, Federation International of Gynecology and Obstetrics.

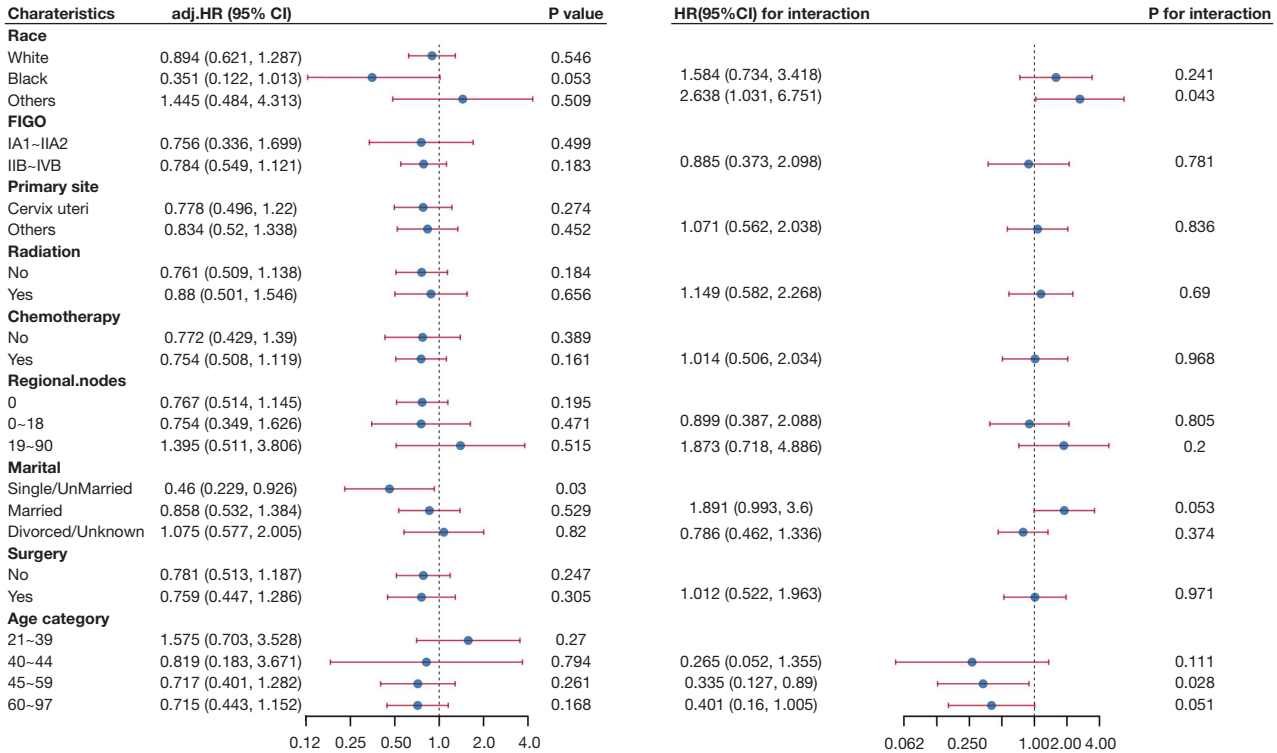

Figure 3 Forest plot of the HRs of the EC patients compared to the AC patients in the subgroup analysis of DSS in the unmatched cohort. EC, cervical endometrioid adenocarcinoma; AC, ordinary cervical adenocarcinoma; DSS, disease-specific survival; adj.HR, adjusted HR; FIGO, Federation International of Gynecology and Obstetrics.

histology of AC patients with that of EC patients to control for potential confounding effects and ensure the reliability of our findings. When OS was the outcome variable, after PSM, a group of 560 patients with cervical cancer, including 280 AC patients and 280 EC patients, were included in the further analysis. When DSS was the outcome variable, after matching, a group of 548 patients with cervical cancer, including 273 AC patients and 275 EC patients, were included in the further analysis. The distribution of the demographic and clinical characteristics was well-balanced in the matched cohort (see *Tables 1*,*2*, Figure S2A,S2B).

According to the Kaplan-Meier analysis, the EC patients had a better prognosis in terms of OS and DSS than the AC patients, but no significant differences were observed between the EC and AC patients in terms OS (P=0.687) and DSS in the matched groups (P=0.507) (see *Figure 4A*,*4B*). The 3- and 5-year OS rates were 83.38% and 75.64% for the EC patients, and 82.81% and 74.66% for the AC patients, respectively. The 3- and 5-year DSS rates were 84.93% and 79.69% for the EC patients, 83.97% and 76.78% for the AC patients, respectively.

In the multivariate analysis (see Figure S3). The variables of race (Black *vs.* White), FIGO stage, radiation, chemotherapy, regional nodes (19–90 *vs.* 0), positive nodes (3–23 *vs.* 0), surgery, and age (60–97 *vs.* 21–39) retained independent significance in terms of OS. The variables of FIGO stage, radiation, regional nodes (19–90 *vs.* 0 group), and surgery retained independent significance in terms of DSS (see Figure S4), However, no statistically significant differences were observed between the EC and AC patients in terms of OS (P=0.851) and DSS (P=0.765). In the multivariate analysis of the matched groups, the histology subtype was not independently associated with OS and DSS in the multivariate Cox model.

Subgroup analysis of matched groups

We conducted subgroup analyses and interaction tests to determine the OS differences between the EC and AC patients stratified according to various characteristics after PSM. No significant differences were observed in any of the variables or subtypes, but the interaction tests revealed

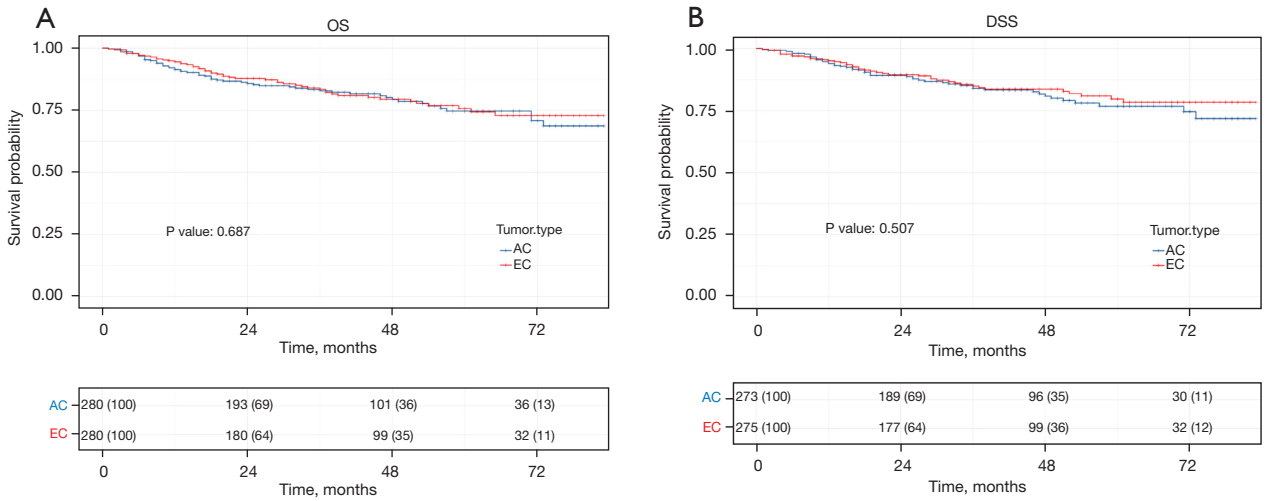

Figure 4 Kaplan-Meier plot and log-rank test of OS (A) and DSS (B) in the matched cohort. AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; OS, overall survival; DSS, disease-specific survival.

that marital status may be an effect modifier (P=0.039) of OS between EC and AC patients. In relation to the analysis comparing DSS between EC and AC patients after PSM, the matched EC patients only exhibited worse survival than the matched AC patients in the other race group (HR =165.29; 95% CI: 37.08–736.76; P<0.001). No significant differences were observed in relation to the other variables (see *Figure 5*).

Discussion

The histological classification of the vast majority of AC cases lacks guidance in relation to treatment modalities. Debate continues as to whether histologic type is an independent prognostic factor, and the survival outcomes of EC patients have rarely been reported. Similarly, very few studies have been conducted comparing the survival outcomes of EC and AC patients. Thus, to accurately evaluate the prognostic effect of EC, we performed 1:1 PSM and subgroup analyses to compare the survival outcomes of cervical EC and AC patients from the SEER database. The preliminary results of our study indicated that EC patients have better survival outcomes than AC patients. Specifically, EC patients had significantly better DSS than AC patients, but no statistically significant difference was observed for OS. The multivariate analysis revealed that the histology subtype of EC or AC was not independently associated with OS and DSS, but EC patients were predicted to have a better prognosis than AC patients. The PSM and subgroup analyses also yielded similar survival outcomes in the matched groups of the EC patients and AC patients, and the EC patients only had worse DSS than the matched AC patients in the other race subgroup (HR =165.29). The interaction test revealed that marital status may be an effect modifier (P=0.039) of OS between EC and AC patients.

A previous study has examined different histological subtypes of cervical AC; for example, Kojima showed that the 5-year DSS rate of gastric-type endocervical adenocarcinoma (ECA) patients was significantly lower than that of non-gastric type ECA patients (30% *vs.* 77%, P<0.0001) (19). More recently, Karamurzin *et al.* reported that DSS rate at 5 years was 42% for gastric-type ECAs and 91% for usual-type ECAs (20). A recent report validating the International Endocervical Adenocarcinoma Criteria and Classification (IECC)criteria included 82 ECAs from a single institution and showed that NHPVAs had significantly higher frequencies of destructive invasive patterns (P=0.009) and advanced-stage ECA (P<0.001). NHPVA patients were observed to have worse recurrence-free survival (RFS) and DSS than HPV-related adenocarcinoma (HPVA) patients (21). Above results were inconsistent with our results. In our study, EC was not found to be associated with high-risk HPV infection, but AC was found to be associated with high-risk HPV infection. However, our analysis revealed that there was no statistically significant difference in the survival outcomes of OS and DSS between the EC and AC patients, but the EC patients showed better survival than the AC patients.

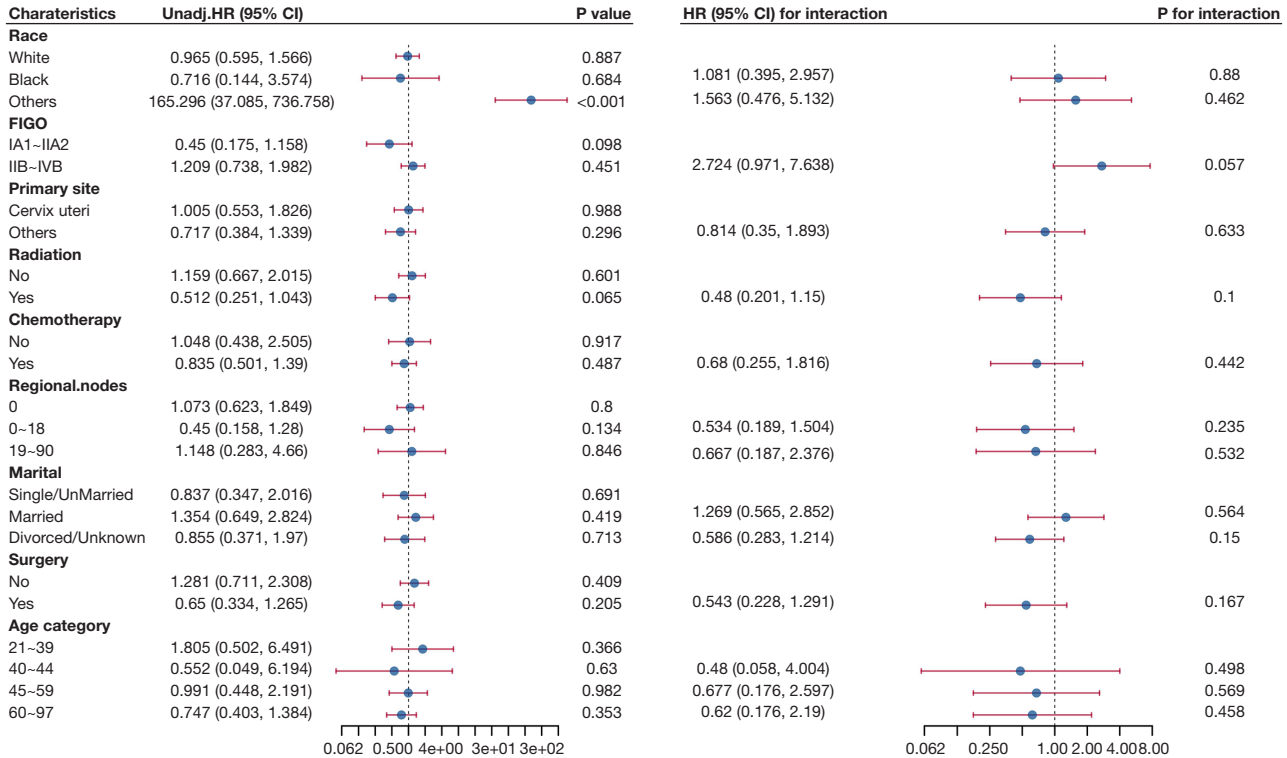

Figure 5 Forest plot of the HRs of the EC patients compared to the AC patients in the subgroup analysis of the matched groups for DSS. EC, cervical endometrioid adenocarcinoma; AC, ordinary cervical adenocarcinoma; DSS, disease-specific survival; unadj.HR, unadjusted HR; FIGO, Federation International of Gynecology and Obstetrics.

Similar to our findings, Chen found that villo-glandular AC has a favorable prognosis (22). We speculated that a number of possible factors may explain these inconsistent results. First, the study populations vary from study to study. Our study population comprised participants with all stages of EC and AC. Conversely, some studies only enrolled patients with partial staging of cervical cancer. Second, in our study, due to the rarity of cervical AC after PSM and subgrouping, the number of the subgroup patients with cervical AC in some groups was very low, which may have affected the statistical significance of the results. Third, different statistical methods were used in different studies. Finally, most previous research studies were not large-sample, multicenter studies.

To further evaluate the relationship between EC and AC, we performed PSM subgroup analyses. Few studies have sought to determine whether histological subtype has an effect on the OS and DSS of EC and AC patients. Knowledge about cervical EC is currently limited to small-case series studies of patients with unclear clinicopathological features, who have received the same treatment (23,24). Some investigators, using a PSM analysis based on the SEER Program data of cervical cancer, found that histology is not an independent factor predicting OS after PSM (25). To date, surgery remains the first choice of treatment for patients with FIGO stage IA1–IIA2. At this stage, after satisfactory surgical therapy, survival is not significantly affected by histological subtype (26). However, in the distant metastasis stage, the prognosis of patients remains poor despite significant advancements in cervical cancer treatment. For patients with regional disease, which includes FIGO stages IIB–IVB, the standard treatment is radiotherapy with concurrent chemotherapy.

In our study, no significant differences were observed between the EC and AC patients in terms of OS and DSS in the initial matched groups, and no significant differences for OS were observed between the EC and AC patients in each subgroup, including in relation to the FIGO stage, radiation, chemotherapy, and surgery. This may explain why the survival of EC and AC patients was similar in every subgroup, including in relation to the FIGO stage, radiation, chemotherapy, and surgery.

The primary causes of treatment failure are local recurrence and distant metastases. In the IECC study, the vast majority of EC patients were HPV negative (12) while the vast majority of AC patients were HPV positive. EC was not sensitive to radiotherapy in the other race subgroup which include more distant cases in this study. EC patients exhibited worse survival than AC patients for DSS. The matched EC patients only exhibited worse survival than the matched AC patients in the other race subgroup for DSS (HR =165.29). Thus, race is an independent factor of survival prognosis, and treatment varies by race. The treatments and populations may have been unevenly distributed, and thus need to be further classified and discussed.

Compared to previous studies in similar populations, this study has several unique strengths. Notably, the sample size of the patients was large and thus provided good statistical power. This large population-based analysis, which contained real-world data from multiple cancer registries, may reflect the differences in clinical conditions between EC and AC patients. However, as this study was retrospective, selection bias could not be ruled out. Thus, we used the PSM method to control the effects of possible confounding factors and create well-matched cohorts. The different subgroups analyzed were stratified by AC and EC histological subtype; thus, we stratified analysis the data better and generated reliable conclusions in this study.

However, we also acknowledge that our study had several limitations, First, the SEER database is a retrospective population-based cohort study database, and has some inevitable limitations that are common to all retrospective database analyses. For example, the SEER database contains no information about recurrence and other prognostic factors. Second, the database did not include any specific details regarding radiotherapy and chemotherapy. Third, the number of EC patients in the subgroup analyses was low, which affected the statistical significance of our findings. In this research, we excluded 92,680 (97.32%) patients based on the exclusion criteria (see above), which might have resulted in selection bias. Third, our study population was composed of participants with all stages of cervical cancer. Some studies only enrolled patients with early stage cervical cancer (27), while others enrolled patients with locally advanced cervical cancer. Fourth, we did not exclude the effect of different treatments on the prognosis of the two pathological types. In addition, while the PSM method minimized the effects of confounding factors, the level of evidence was still lower than a randomized controlled clinical trial. Given these limitations, additional prospective, randomized controlled trials need to be conducted to minimize confusion and confirm these findings.

Finally, on the basis of these results, while there were no statistically significant differences in OS and DSS between the EC and AC patients, significant differences were observed in the other race subgroup for DSS. Our HR study revealed that EC patients had better survival than AC patients. Some research has suggested that the prognosis of each AC varies according to its histopathological type (12,22,28-30). Some investigators have suggested that different subtypes of cervical AC may be different at the molecular level (31,32), Taken as a whole, from a clinical point of view, our results suggest that EC may be associated with better survival than AC even after PSM. However, these results need to be confirmed in prospective studies with large-sample sizes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1180/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1180/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Univariate and multivariate analyses of the unmatched cohort for OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Race: Black *vs.* White	1.006 (0.834–1.214)	0.947	0.947 (0.784–1.144)	0.571
Race: Other *vs.* White	0.394 (0.324–0.478)	<0.001	0.633 (0.518–0.775)	<0.001
FIGO: IIB–IVB *vs.* IA1–IIA2	13.327 (10.613–16.735)	<0.001	5.996 (4.43–8.115)	<0.001
Primary site: other *vs.* cervix uteri	0.684 (0.579–0.809)	<0.001	0.849 (0.715–1.007)	0.06
Radiation: yes *vs.* no	0.9 (0.735–1.101)	0.306	1.481 (1.122–1.954)	0.005
Chemotherapy: yes *vs.* no	3.751 (3.133–4.49)	<0.001	0.561 (0.454–0.693)	<0.001
Regional nodes: 0–18 *vs.* 0	0.24 (0.19–0.304)	<0.001	0.507 (0.357–0.72)	<0.001
Regional nodes: 19–90 *vs.* 0	0.124 (0.088–0.176)	<0.001	0.271 (0.171–0.43)	<0.001
Positive nodes: 0–2 *vs.* 0	1.307 (0.919–1.86)	0.136	1.507 (0.938–2.421)	0.09
Positive nodes: 3–23 *vs.* 0	2.245 (1.524–3.307)	<0.001	2.385 (1.436–3.96)	<0.001
Marital: married *vs.* single/unmarried	1.254 (1.076–1.461)	0.004	1.005 (0.858–1.178)	0.949
Marital: divorced/unknown *vs.* single/unmarried	1.43 (1.246–1.641)	<0.001	1.14 (0.99–1.313)	0.068
Surgery: yes *vs.* no	0.119 (0.099–0.143)	<0.001	0.428 (0.321–0.569)	<0.001
Age category: 40–44 *vs.* 21–39	1.129 (0.76–1.678)	0.548	1.029 (0.689–1.536)	0.89
Age category: 45–59 *vs.* 21–39	2.385 (1.782–3.193)	<0.001	1.51 (1.116–2.043)	0.007
Age category: 60–97 *vs.* 21–39	7.311 (5.568–9.6)	<0.001	2.912 (2.171–3.905)	<0.001
Tumor type: EC *vs.* AC	0.786 (0.589–1.048)	0.1	0.838 (0.624–1.124)	0.238

AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; FIGO, Federation International of Gynecology and Obstetrics; OS, overall survival.

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Table S2 Univariate and multivariate analyses of the unmatched cohort for DSS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Race: Black *vs.* White	1.008 (0.824–1.233)	0.938	0.973 (0.795–1.191)	0.789
Race: Other *vs.* White	0.406 (0.33–0.501)	<0.001	0.662 (0.533–0.823)	<0.001
FIGO: IIB–IVB *vs.* IA1–IIA2	16.927 (12.978–22.077)	<0.001	7.306 (5.172–10.319)	<0.001
Primary site: other *vs.* cervix uteri	0.689 (0.577–0.825)	<0.001	0.856 (0.713–1.027)	0.094
Radiation: yes *vs.* no	0.871 (0.7–1.083)	0.213	1.421 (1.044–1.932)	0.025
Chemotherapy: Yes *vs.* No	4.285 (3.516–5.224)	<0.001	0.596 (0.474–0.75)	<0.001
Regional nodes: 0–18 *vs.* 0	0.216 (0.167–0.281)	<0.001	0.444 (0.296–0.667)	<0.001
Regional nodes: 19–90 *vs.* 0	0.107 (0.072–0.158)	<0.001	0.244 (0.144–0.412)	<0.001
Positive nodes: 0–3 *vs.* 0	1.419 (1.014–1.985)	0.041	1.783 (1.085–2.93)	0.022
Positive nodes: 4–23 *vs.* 0	2.507 (1.522–4.129)	<0.001	2.79 (1.497–5.199)	0.001
Marital: married *vs.* single/unmarried	1.164 (0.988–1.37)	0.069	0.956 (0.808–1.132)	0.603
Marital: divorced/unknown *vs.* single/unmarried	1.442 (1.244–1.67)	<0.001	1.14 (0.981–1.326)	0.088
Surgery: yes *vs.* no	0.105 (0.085–0.129)	<0.001	0.42 (0.306–0.576)	<0.001
Age category: 40–44 *vs.* 21–39	1.095 (0.727–1.649)	0.665	0.96 (0.634–1.454)	0.848
Age category: 45–59 *vs.* 21–39	2.296 (1.7–3.101)	<0.001	1.364 (0.998–1.864)	0.051
Age category: 60–97 *vs.* 21–39	6.499 (4.898–8.623)	<0.001	2.361 (1.74–3.204)	<0.001
Tumor type: EC *vs.* AC	0.724 (0.526–0.997)	0.048	0.809 (0.584–1.121)	0.203

AC, ordinary cervical adenocarcinoma; EC, cervical endometrioid adenocarcinoma; FIGO, Federation International of Gynecology and Obstetrics; DSS, disease-specific survival.

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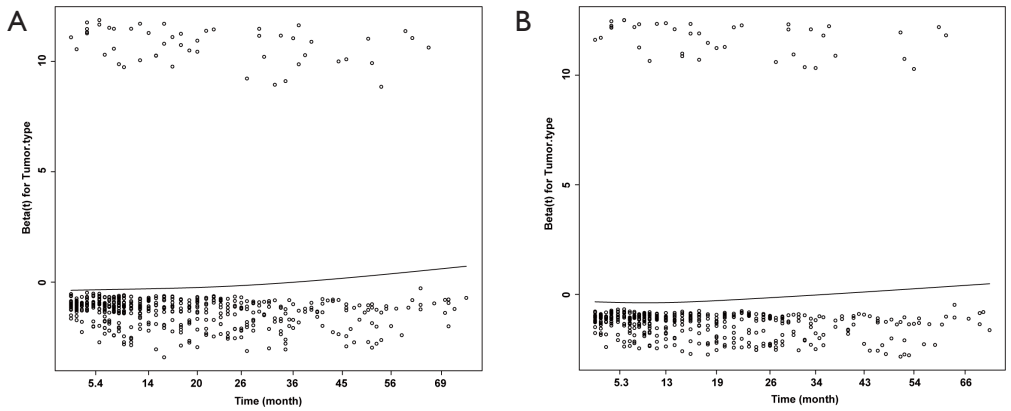

Figure S1 Residual diagram of the PH tests for OS and DSS (A,B). OS, overall survival; DSS, disease-specific survival.

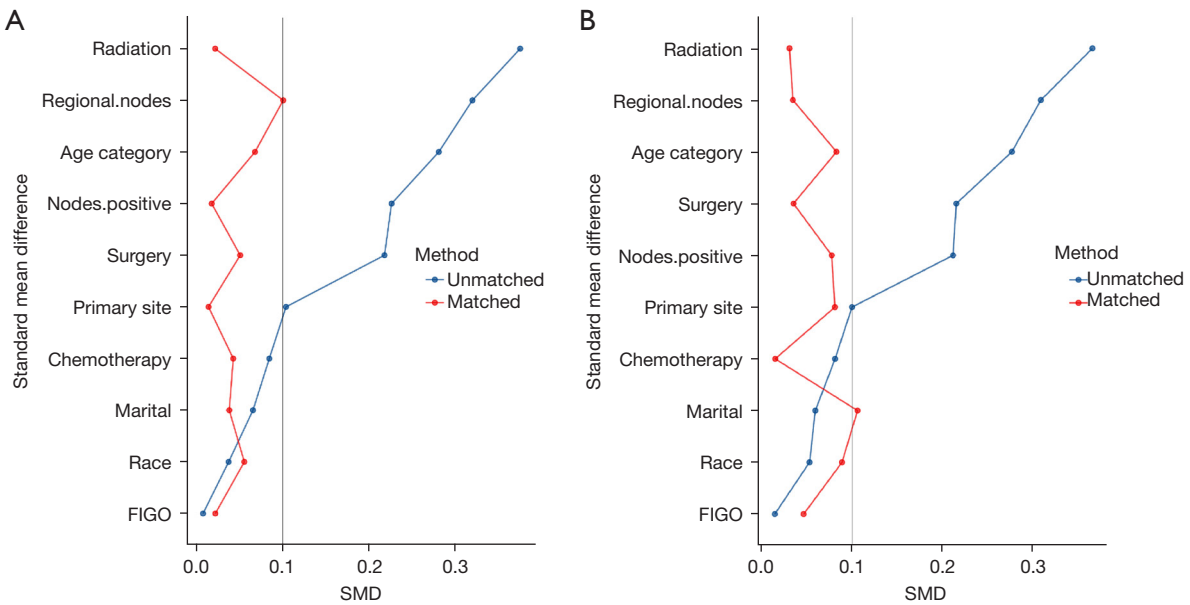

Figure S2 Balance tests of the baseline data before and after PSM (A,B). FIGO, Federation International of Gynecology and Obstetrics; SMD, standard mean difference.

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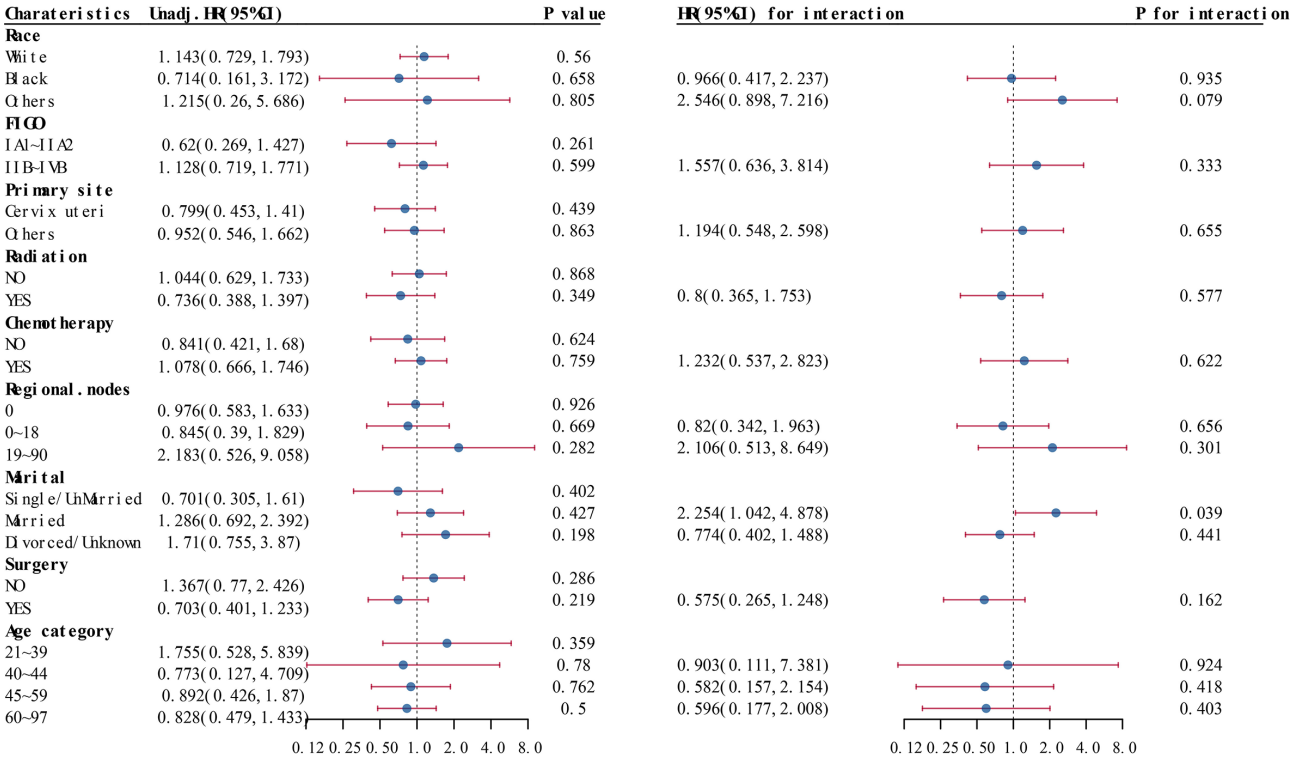

Figure S3 Forest plot of the HRs comparing the EC and AC patients in the multivariate analyses in the matched cohort for OS. EC, cervical endometrioid adenocarcinoma; AC, ordinary cervical adenocarcinoma; OS, overall survival.

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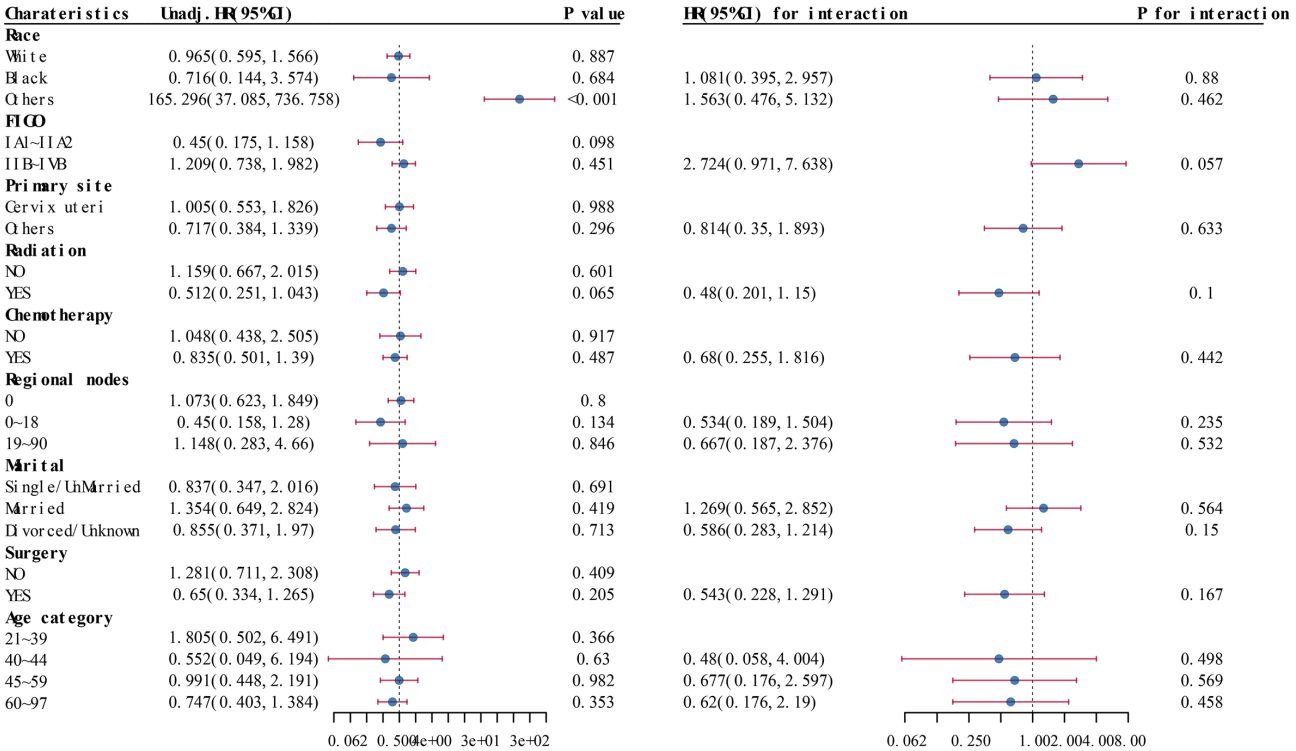

Figure S4 Forest plot of the HRs comparing the EC and AC patients in the multivariate analyses in the matched cohort for DSS. EC, cervical endometrioid adenocarcinoma; AC, ordinary cervical adenocarcinoma; DSS, disease-specific survival.

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