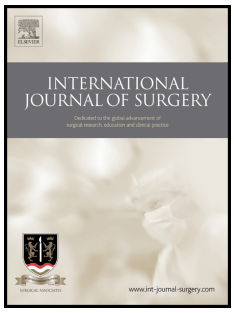
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The prognostic value of histologic subtype in node-positive early-stage cervical cancer after hysterectomy and adjuvant radiotherapy

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The prognostic value of histologic subtype in node-positive early-stage cervical cancer after hysterectomy and adjuvant radiotherapy

Running head: Cervical Cancer Histological Prognosis

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The prognostic value of histologic subtype in node-positive early-stage cervical cancer after hysterectomy and adjuvant radiotherapy

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ABSTRACT

Background: To assess the survival outcomes in patients with International Federation of Gynecology and Obstetrics (FIGO) stage I–IIA adenocarcinoma (AC) or squamous cell carcinoma (SCC) of the uterine cervix after hysterectomy and adjuvant radiotherapy (RT).

Methods: Patients with a primary diagnosis of FIGO stage I–IIA AC or SCC of the uterine cervix after hysterectomy and adjuvant RT between 1988 and 2012 were included using data from the Surveillance, Epidemiology, and End Results database. Univariate and multivariate Cox regression analyses were used to analyze the effect of histologic subtype on cause-specific survival (CSS) and overall survival (OS).

Results: We included 1171 patients: 919 with cervical SCC and 252 with cervical AC. In multivariate analysis, cervical AC was an independent adverse prognostic factor for survival. Patients with cervical AC had worse CSS (p = 0.001) and OS (p = 0.001) compared to patients with cervical SCC. In the subgroup analysis, patients with cervical SCC in the era of concurrent chemoradiotherapy (CCRT) (2000–2012) had better CSS (p = 0.006) and OS (p = 0.004). However, there was no significant difference in CSS (p = 0.079) and OS (p = 0.053) between the eras of RT (1988–1999) and CCRT for patients with cervical AC.

Conclusions: Survival of cervical AC is significantly worse than that of cervical SCC. As CCRT usage increases, the survival benefit is derived only in cervical SCC, but not in cervical AC.

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Keywords: Cervical cancer, Squamous cell carcinoma, Adenocarcinoma, Radiotherapy, Survival

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1. Introduction

Cervical cancer (CC) remains an important public women's health problem worldwide [1]. Squamous cell carcinoma (SCC) is the most common histologic subtype of CC. The incidence of adenocarcinoma (AC) has increased markedly in recent decades, and it comprises approximately 20–25% of all CC [2-4]. The epidemiology, clinicopathological and molecular characteristics, and patterns of failure of AC of the uterine cervix differ from that of SCC of the uterine cervix [5-8]. However, whether survival of cervical AC differs from that of cervical SCC is a controversial topic.

The treatment recommendation for cervical AC in the current National Comprehensive Cancer Network (NCCN) guideline is similar to that of cervical SCC [9]. Cervical AC tends to be more aggressive compared to cervical SCC irrespective of the primary treatment [7,10,11]. Several studies, including ours, have found significantly worse survival of patients with cervical AC than in patients with cervical SCC who received definitive radiotherapy (RT)/radiochemotherapy [11-14]. Therefore, AC of the uterine cervix may be less responsive to RT/radiochemotherapy compared with cervical SCC.[15] However, the difference in survival outcomes of the AC and SCC subtypes of CC in patients who have undergone radical surgery remains controversial. Some studies have found no significant difference in survival of SCC and AC in early-stage CC [4,16-18]. In contrast, others have found that patients with cervical AC had poor prognosis [7,19]. The differing primary treatment strategies for different International Federation of Gynecology and Obstetrics (FIGO) stages may influence the survival outcomes. In our previous study based on the Surveillance, Epidemiology, and End Results (SEER)

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database, AC was an independent adverse prognostic factor in patients with CC who received definitive RT [14]. In this study, we focused on patients with CC who had undergone hysterectomy and adjuvant RT, and examined whether there were differences in survival outcomes between patients with cervical AC and SCC.

2. Materials and methods

2.1. Patients

Patients with a primary diagnosis of CC between 1988 and 2012 were included using the SEER database [20]. Among these patients, we selected patients according to the following criteria: SCC and AC of the uterine cervix; FIGO stage I–IIA disease; pathological diagnosis of positive lymph nodes; without preoperative RT; history of hysterectomy with lymph node dissection followed by adjuvant beam RT. The ethics committees of the XXXXXX approved this study.

2.2. Demographic and Clinicopathological Factors

The following variables were extracted from the SEER database: age, year of diagnosis, race/ethnicity, tumor grade, histologic subtype, tumor size, FIGO stage, marital status, and survival. The primary endpoint was cause-specific survival (CSS) and overall survival (OS). As the recommendation for concurrent chemoradiotherapy (CCRT) was made after 2000 [21,22], subgroup analysis was compared for patients diagnosed in the prior years (1988–1999) and the later years (2000–2013). Patients diagnosed between 1988 and 1999 were assumed to have been treated with RT and less frequently with

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chemotherapy, while patients diagnosed between 2000 and 2012 were assumed to have been treated more often with CCRT.

2.3. Statistical analysis

All statistical analyses were performed using the SPSS statistical software package (version 21.0; IBM Corporation, Armonk, NY, USA). Comparisons between histologic subtypes in the compared demographic and clinicopathological characteristics were analyzed by the chi-square test, except for continuous variables, for which analysis of variance was used. The survival curves were calculated and compared using the Kaplan–Meier method and log-rank tests, respectively. Univariate and multivariate Cox regression analyses were used to explore the risk factors for CSS and OS. $p < 0.05$ was considered significant for all analyses.

3. Results

We included 1171 patients; the median age was 42 years (range, 20–84 years). Specifically, we analyzed 919 patients (78.5%) with cervical SCC and 252 patients (21.5%) with cervical AC. Table 1 shows the demographic and clinicopathological characteristics. Patients with cervical AC tended to be older (median age, 44.5 years vs. 41.0 years, $p = 0.001$) and had more well-differentiated tumors (15.7% vs. 2.1%, $p < 0.001$) than patients with cervical SCC. Year of diagnosis, race/ethnicity, tumor size, FIGO stage, lymph node status, and marital status were not significantly different between cervical SCC and AC. The univariate analysis showed that patients diagnosed in

1988–1999, who were older, had AC, FIGO stage II disease, larger tumors, and higher number of positive lymph nodes had worse CSS and OS (Table 2). Ethnicity, tumor grade, and marital status did not affect survival.

Multivariate analysis (Table 3) also indicated that AC was an independent prognostic factor of survival. Patients with cervical AC had worse CSS (hazard ratio [HR] = 1.614, 95% confidence interval [CI] 1.207–2.159, $p = 0.001$) and OS (HR = 4.474, 95% CI 1.114–1.951, $p = 0.001$) compared to patients with cervical SCC. The 5-year CSS rate of cervical SCC and AC was 80.1% and 70.5%, respectively (log-rank tests, $p < 0.001$); the 5-year OS rate was 78.1% vs. 70.1%, respectively (log-rank tests, $p < 0.001$) (Figure 1a & 1b). The other independent adverse prognostic factors were diagnosis in 1988–1999, older age, FIGO stage II disease, larger tumor, and higher number of positive lymph nodes.

After 2000, CCRT became the standard treatment for node-positive CC after radical surgery [21,22]. We analyzed the survival of the different histologic subtypes of CC in the eras of RT (1988–1999) and CCRT (2000–2012). Patients with cervical SCC had better CSS ($p = 0.006$) and OS ($p = 0.004$) in the CCRT era. However, there was no significant difference in CSS ($p = 0.079$) and OS ($p = 0.053$) for patients with cervical AC between the eras of RT and CCRT.

4. Discussion

In this study, we assessed the effect of histologic subtype on survival in patients with node-positive CC who had undergone hysterectomy and postoperative adjuvant RT.

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Our results suggest that the AC subtype is an independent adverse prognostic factor that significantly affects survival in CC, and survival of cervical AC was significantly worse than that of cervical SCC. Despite being a retrospective analysis, this study represents a population-based study, which might help us understand the survival differences between different histologic subtypes in CC and design optimal treatment strategies accordingly.

The incidence of cervical AC has increased in recent decades. However, early diagnosis of cervical AC is difficult. AC of the uterine cervix tends to infiltrate the deep stroma, involving the lymphovascular space, and with subsequent lymph node metastasis and distant metastasis. Therefore, cervical AC may be more aggressive than cervical SCC. Currently, comparisons of the clinicopathological characteristics of cervical SCC and AC histology have yielded inconsistent results. Noh et al. found that more patients with cervical AC were diagnosed at a younger age and at the early stage compared to patients with cervical SCC, but there were no significant differences in parametrial invasion, lymphovascular invasion, stromal invasion, and surgical margins [19]. Park et al. showed that patients with cervical AC tended to be younger and have lymphovascular invasion. However, there were no significant differences in clinicopathological factors, which included tumor stage, grade and size; parametrial invasion; stromal invasion; nodal status; and surgical margins [8]. Three other studies also reported no significant differences between the clinicopathological factors and treatment modalities of cervical AC and SCC [17,18,23]. In our study, cervical AC more likely to be diagnosed in older patients and be well-differentiated; more patients with cervical SCC had poorly/undifferentiated tumors and were younger. However, we could not obtain the data on parametrial invasion,

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lymphovascular invasion, stromal invasion, and surgical margins due to the lack of the corresponding data in the SEER database.

Survival of cervical AC was significantly worse than that of cervical SCC in patients who received definitive RT/CCRT, suggesting that the radiosensitivity of cervical AC may be lower than that of cervical SCC [11-15]. However, the survival outcomes between cervical AC and SCC in patients who undergo radical surgery remain controversial. A population-based epidemiological study by Nogueira-Rodrigues et al. found that the initial therapeutic response was similar in patients with the AC and SCC subtypes [16]. Others have also found that survival in patients with early-stage cervical AC was similar to that of patients with cervical SCC who underwent radical surgery [4,17,18]. However, Noh et al. found that cervical AC was associated with worse survival in patients with FIGO stage IB–IIA CC after surgical resection and adjuvant RT [19]. Huang et al. also found that compared with cervical SCC, cervical AC/adenosquamous carcinoma was an independent risk factor for patients with CC who underwent radical surgery and adjuvant RT [7]. It is important to note that patients in both of the above studies had high risk factors for recurrence and received postoperative RT [7,19], whereas Winer et al., Teke et al., and Mabuchi et al. included all patients with FIGO stage I–II disease, and not all patients need adjuvant RT [4,17,18]. Therefore, the differences in adjuvant therapy may be responsible for the differences in survival outcome. In this study, we included patients with positive lymph nodes after radical resection and postoperative RT. Our results also suggest that survival in cervical AC was significantly worse than that in cervical SCC. A randomized trial comparing patients with

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FIGO stage IB–IIA CC treated with surgery or RT reported equivalent survival rates. However, patients with cervical AC treated with hysterectomy had better disease-free survival than patients treated with definitive RT (66% vs. 47%, p = 0.02) [24]. These findings also suggest that cervical AC may be resistant to RT.

Based on two randomized trials, the standard treatment since 2000 for patients with CC with high risk factors after radical surgery has been CCRT [21,22]. The epidemiology, clinicopathological and molecular characteristics, and patterns of failure differ between the AC and SCC subtypes in CC. However, the treatment recommendation in the current NCCN guideline for cervical AC is similar to that of cervical SCC. Chemotherapy may yield greater benefits in cervical AC because cervical AC is more aggressive compared to cervical SCC. Cervical AC is also resistant to chemotherapy [15]. However, the efficacy of chemotherapy in cervical AC is still controversial. Shimada et al. reported favorable 5-year OS rates for chemotherapy rather than RT/CCRT or RT followed by chemotherapy (79.2% vs. 70.9% vs. 66.2%) [25]. A subgroup analysis of the Southwest Oncology Group 8797 trial showed that patients with cervical AC had worse progression-free survival (PFS) compared to patients with cervical SCC who received RT, suggesting lower radiosensitivity of cervical AC compared to cervical SCC. However, this difference did not reach statistical significance through the addition of concurrent chemotherapy to RT [22]. Huang et al. found that CCRT improved survival for intermediate-risk patients with cervical AC (without parametrial invasion or lymph node metastasis), but not necessarily for patients in the high-risk group (with parametrial invasion or lymph node metastasis) [7]. However, Seki et al. reported that PFS was

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significantly worse in patients with cervical AC who received RT/CCRT compared to patients with SCC who were treated with RT/CCRT (p = 0.002). Therefore, adjuvant RT/CCRT may be less effective for patients with cervical AC than for patients with cervical SCC [23]. A study from China also suggested that CCRT does not improve survival in cervical AC [26].

In this study, we analyzed the survival of different histologic subtypes of CC in the eras of RT (1988–1999) and CCRT (2000–2012). Our results suggest that survival of cervical SCC in the CCRT era is significantly better compared to that of the RT era. However, the year of diagnosis did not have an effect on survival in cervical AC. In previous studies and the current NCCN guideline treatment recommendations, chemotherapy regimens were mainly cisplatin-based. Huang et al. suggested that cisplatin-based CCRT did not show survival benefit and changed the CCRT regimen to a taxane-based regimen [13]. As taxane-based regimens have shown improved effectiveness for cancer with non-SCC histology [27,28], further studies are needed to establish the role of new systemic treatment regimens.

There was no difference in local control rate between early-stage cervical AC and SCC after hysterectomy, where the rate for both was approximately 90% [7,8]. However, patients with cervical AC had higher distant recurrence rates than patients with cervical SCC [7,8]. Seki et al. found that, after surgical resection followed by RT, intraperitoneal recurrence (8.7% vs. 2.2%) and extrapelvic recurrence (26.1% vs. 12.2%) were higher in patients with cervical AC than in patients with cervical SCC (p = 0.091) [23]. Therefore, more treatment strategies are needed to reduce the risk of distant metastasis of cervical

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AC.

There are several limitations in this study. First, the retrospective design has potential confounding biases in the analysis. Second, risk factors such as parametrial invasion, lymphovascular invasion, stromal invasion, and margin status were unknown in the SEER database. Third, we could not obtain the chemotherapy data from the SEER database. In addition, local and distant recurrence data were also lacking.

5. Conclusion

In conclusion, our results suggest that the AC subtype of CC is an independent adverse prognostic factor in patients with node-positive early-stage CC who received radical surgery and adjuvant RT. The survival of cervical AC is significantly worse than that of cervical SCC. As CCRT usage increases, the survival benefit is only reflected in cervical SCC, and not in cervical AC. New treatment strategies for cervical AC require further exploration.

Ethical approval

The study was approved by the ethics committee of the XXXXXX.

Author contribution

All authors finally approved the submitted version.

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Conflict of interest disclosures

The authors have no conflicts of interest to disclose.

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Figure legends

Figure 1. Impact of histologic subtype on CSS (A) and OS (B) in CC.

Figure 2. Impact of year of diagnosis on CSS (A) and OS (B) in cervical SCC.

Figure 3. Impact of year of diagnosis on CSS (A) and OS (B) in cervical AC.

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Table 1. Patient characteristics

Characteristic	n	SCC (%)	AC (%)	*p*
Year of study				
1988–1999	341	275 (30.0)	66 (26.2)	0.248
2000–2012	830	644 (70.0)	186 (73.8)	
Age (years)				
Median ± SD	42 ± 11.9	41.0 ± 11.5	44.5 ± 13.0	0.001
<50	856	691 (75.2)	165 (65.5)	0.003
50–69	268	198 (21.5)	70 (27.8)	
≥70	47	30 (3.3)	17 (6.7)	
Race				
White	942	742 (80.7)	200 (79.4)	0.687
Black	96	72 (7.8)	24 (9.5)	
Other and unknown	133	105 (11.4)	28 (11.1)	
Grade (n = 1077)				
G1	55	18 (2.1)	37 (15.7)	<0.001
G2	468	361 (42.9)	107 (45.3)	
G3–4	554	462 (54.9)	92 (39.0)	
FIGO stage				
I	1039	819 (89.1)	220 (87.3)	0.419
II	132	100 (10.9)	32 (12.7)	
Largest tumor diameter (median ± SD, cm) (n = 950)	33 ± 17.8	32 ± 17.9	35 ± 17.3	0.657
Positive lymph nodes (median ± SD) (n)	2.0 ± 2.5	2.0 ± 2.6	2.0 ± 2.3	0.444
Marital status (n = 1118)				
Single	493	393 (44.7)	100 (42.0)	0.466
Married	625	487 (55.3)	138 (58.0)	

Abbreviations: AC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; SCC, squamous cell carcinoma; SD, standard deviation.

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Table 2. Univariate Cox regression analysis of prognostic factors.

Characteristic	CSS			OS		
	HR	95%CI	*p*	HR	95%CI	*p*
Year of diagnosis						
1988–1999	1			1		
2000–2012	0.683	0.537–0.869	0.002	0.682	0.543–0.856	0.001
Age (years)						
<50	1			1		
50–69	1.582	1.221–2.050	0.001	1.685	1.325–2.142	<0.001
≥70	1.795	1.042–3.092	0.035	2.143	1.323–3.471	
Race						
White	1			1		
Black	1.020	0.669–1.553	0.928	1.127	0.772–1.645	0.536
Other and unknown	1.265	0.894–1.792	0.185	1.233	0.887–1.714	0.214
Grade						
G1	1			1		
G2	0.864	0.494–1.512	0.609	0.812	0.488–1.352	0.424
G3–4	1.148	0.664–1.986	0.621	1.070	0.650–1.761	0.791
Histologic subtype						
SCC	1			1		
AC	1.732	1.346–2.229	<0.001	1.573	1.236–2.003	<0.001
FIGO stage						
I	1			1		
II	2.104	1.558–2.843	<0.001	2.052	1.545–2.727	<0.001
Tumor size	1.019	1.012–1.025	<0.001	1.018	1.012–1.025	<0.001
Positive lymph nodes	1.080	1.055–1.106	<0.001	1.077	1.053–1.103	<0.001
Marital status						
Single	1			1		
Married	1.139	0.894–1.450	0.293	1.002	0.801–1.255	0.983

Abbreviations: AC, adenocarcinoma; CI, confidence interval; CSS, cause-specific survival; FIGO, International Federation of Gynecology and Obstetrics; G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; HR, hazard ratio; SCC, squamous cell carcinoma; OS, overall survival.

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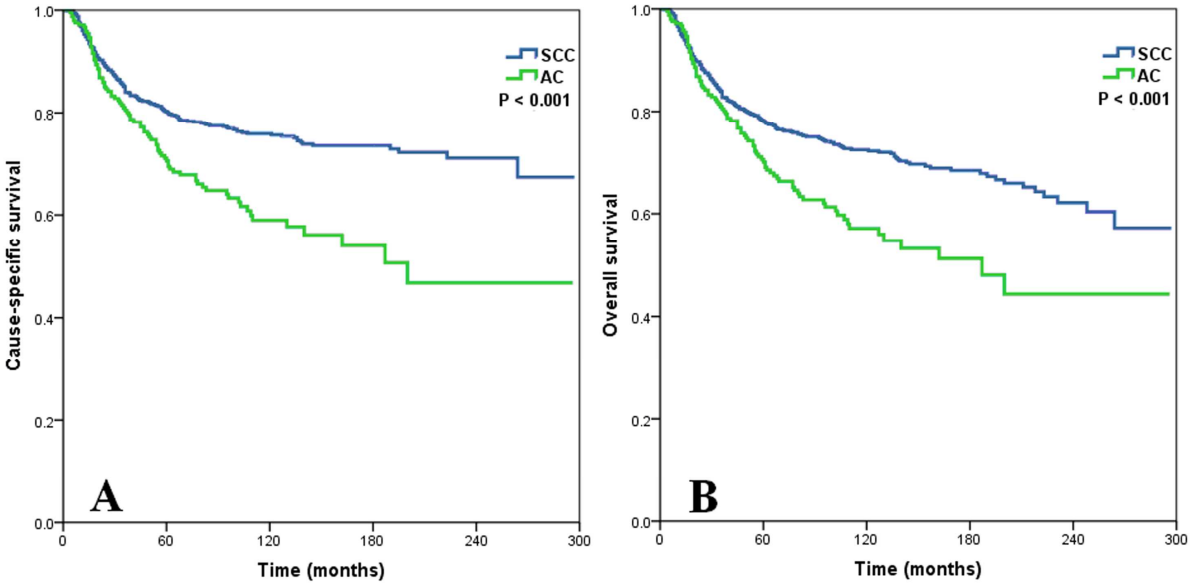
Table 3. Multivariate Cox regression analysis of prognostic factors.

Characteristic	CSS			OS		
	HR	95%CI	*p*	HR	95%CI	*p*
Year of diagnosis						
1988–1999	1			1		
2000–2012	0.684	0.517–0.906	0.008	0.695	0.533–0.906	0.007
Age (years)						
<50	1			1		
50–69	1.357	1.004–1.834	0.047	1.388	1.046–1.843	0.023
≥70	1.611	0.845–3.073	0.148	1.631	0.882–3.017	0.119
Histologic subtype						
SCC	1			1		
AC	1.614	1.207–2.159	0.001	1.474	1.114–1.951	0.007
FIGO stage						
I	1			1		
II	1.859	1.317–2.622	<0.001	1.716	1.231–2.393	0.001
Tumor size	1.015	1.008–1.022	<0.001	1.015	1.009–1.022	<0.001
Positive lymph nodes	1.115	1.068–1.163	<0.001	1.11	1.066–1.157	<0.001

Abbreviations: AC, adenocarcinoma; CI, confidence interval; CSS, cause-specific survival; HR, hazard ratio; SCC, squamous cell carcinoma; OS, overall survival.

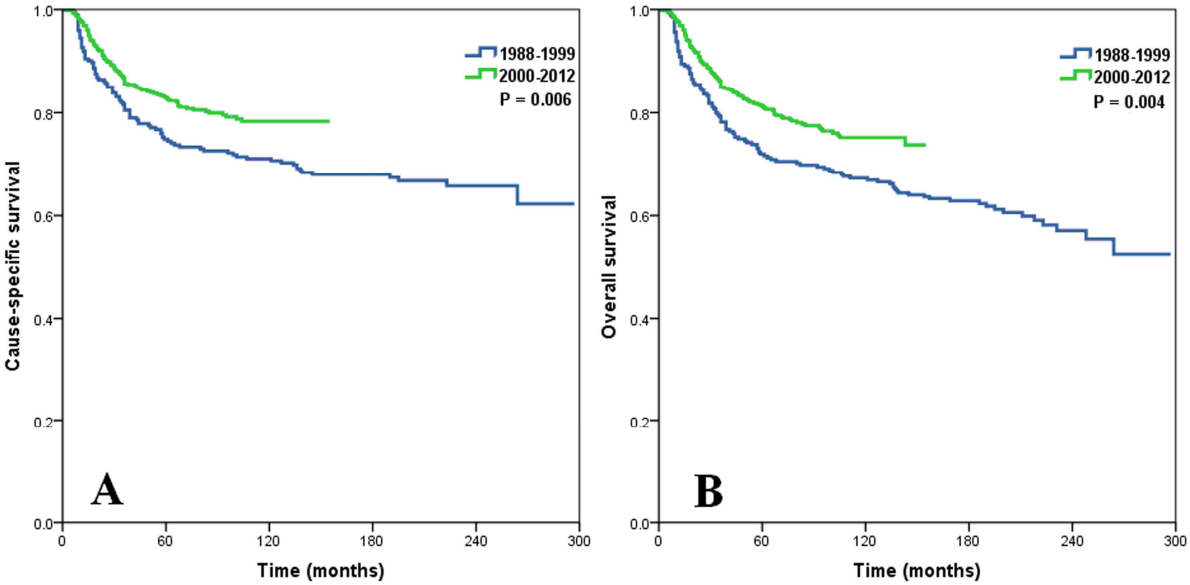
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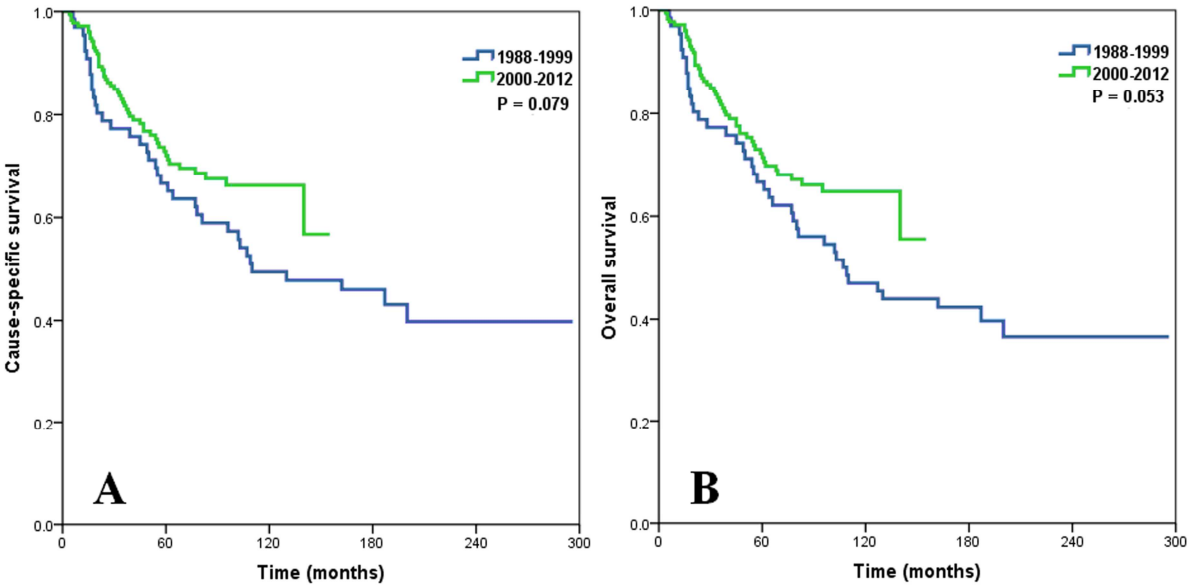
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HIGHLIGHTS

1. Whether survival of cervical AC differs from that of cervical SCC is a controversial topic.
2. Survival of cervical AC is significantly worse than that of cervical SCC in node-positive early-stage CC after hysterectomy and adjuvant RT.
3. As CCRT usage increases, the survival benefit is derived only in cervical SCC, but not in cervical AC.

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