

Comparison of survival outcomes between radical hysterectomy and definitive radiochemotherapy in stage IB1 and IIA1 cervical cancer

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Introduction: There is an ongoing debate regarding the optimal local treatment modalities for stage IB1 and IIA1 cervical cancer. The aim of this study was to determine whether radical hysterectomy or definitive radiochemotherapy is superior in stage IB1 and IIA1 cervical squamous cell carcinoma (SCC).

Methods: From 1990 to 2010, a total of 3,769 patients with stage IB1 and IIA1 cervical SCC were included from the Surveillance, Epidemiology, and End Results database and were stratified according to whether they received radical hysterectomy or primary radiochemotherapy. Propensity score-matching (PSM) methods were used to balance patient baseline characteristics. Cancer-specific survival (CSS) and overall survival (OS) were compared between the two groups.

Results: Of the 3,769 patients, 3,653 (96.9%) and 116 (3.1%) patients received radical hysterectomy and definitive radiochemotherapy, respectively. Radiochemotherapy was rarely used for definitive treatment prior to 2000. Before PSM, patients who were older, of black ethnicity, and with larger tumor size and stage IIA1 disease were more likely to receive definitive radiochemotherapy. A total of 116 pairs were completely matched using PSM. The local treatment modalities had no effect on CSS or OS in either unmatched or matched populations. In the matched population, the 8-year CSS rates were 82.1% and 76.5% in surgery and radiochemotherapy groups, respectively ($p=0.382$). The 8-year OS rates were 74.6% and 67.8% in surgery and radiochemotherapy groups, respectively ($p=0.205$).

Conclusion: Our population-based study suggests that there is no clear local treatment of choice on survival outcomes between radical hysterectomy and definitive radiochemotherapy in patients with stage IB1 and IIA1 cervical SCC.

Keywords: cervical cancer, early stage, hysterectomy, radiotherapy, propensity score matching

Introduction

The incidence of cervical cancer (CC) has steadily declined over the last few decades coincident with the widespread, population-based screening. However, CC remains the third most common cancer in females and the fourth leading cause of cancer-related deaths in females worldwide, especially in low- and middle-income countries.¹⁻³ For patients with locally advanced CC, definitive radiochemotherapy is the standard treatment,⁴ while neoadjuvant chemotherapy + radical surgery was also a choice of treatment.⁵⁻⁸ The standard treatment for stage IB1 and IIA1 CC is radical hysterectomy, whereas radiotherapy (RT) with or without chemotherapy is currently reserved as an optional treatment for nonoperative patients.⁹

Population-based studies have shown that most patients with stage IB–IIA CC underwent radical surgery rather than RT.¹⁰⁻¹² One randomized study found that the

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survival outcomes between radical hysterectomy and primary RT were similar for stage IB–IIA cervical squamous cell carcinoma (SCC), whereas radical surgery was a better choice for patients with cervical adenocarcinoma.¹³ However, there is still ongoing debate regarding the optimal local treatment modalities for early-stage CC. Two previous population-based studies indicated that surgical treatment was associated with significantly better survival outcomes compared with primary RT in stage IB–IIA CC.^{10,11} A recent study of the National Cancer Database indicated that the addition of chemotherapy to definitive RT in stage IB1 and IIA1 CC improved overall survival (OS).¹⁴ The purpose of our study was to determine whether radical hysterectomy or definitive radiochemotherapy was superior in women with stage IB1 and IIA1 CC.

Materials and methods

Patient identification

Female patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB1 and IIA1 CC who were treated between 1990 and 2010 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. SEER is a population-based cancer registry representing approximately 28% of the United States population that is maintained by the National Cancer Institute.¹⁵ Patients who met the following criteria were included: 1) pathologically diagnosed with primary stage IB1 and IIA1 cervical SCC; 2) received either radical hysterectomy or definitive radiochemotherapy as the initial treatment (the RT cohort only included patients who received external-beam RT in combination with implants or isotopes); and 3) had available data for race/ethnicity, tumor grade, tumor size, and nodal status. This study was approved by the ethics committees of the First Affiliated Hospital of Xiamen University.

Statistical methods

Propensity score matching (PSM) was used to reduce selection bias in this study.¹⁶ The propensity score was defined as the probability of being assigned to the radical hysterectomy or definitive radiochemotherapy groups, given the demographic and clinicopathological variables. Propensity scores were computed by logistic regression for each patient with an algorithm of 1:1 matching using the following variables: age, race/ethnicity, tumor grade, FIGO stage, tumor size, and nodal status.¹⁷ Frequency distributions between categorical variables were analyzed by the χ^2 test or Fisher's exact test, and analysis of variance was used to compare differences among the continuous variables. Survival time was plotted using the Kaplan-Meier method and compared using the log-rank test.

The primary endpoints of this study were cancer-specific survival (CSS) and OS. CSS was calculated for patients who died with CC-related disease. OS was defined as the time from treatment initiation until last follow-up or death. Univariate and multivariate proportional hazards models were used to analyze the prognostic factors for CSS and OS. The potential prognostic factors included age (<50 years vs ≥ 50 years), race/ethnicity (white vs black vs other), tumor grade (well/moderately differentiated vs poorly/undifferentiated), tumor size (continuous variables), FIGO stage (IB1 vs IIA1), nodal status (negative vs positive), and treatment modalities (hysterectomy vs radiochemotherapy). The potential prognostic factors were initially compared using univariate analysis, and all variables that were significant in the univariate analysis were entered into the multivariate Cox regression model. Two-sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

Results

There were 3,769 patients with stage IB1 and IIA1 CC identified in this study, including 3,653 (96.9%) and 116 (3.1%) patients who received radical hysterectomy and definitive radiochemotherapy, respectively. Surgery was the most common treatment modality used in patients. The use of radiochemotherapy as a definitive treatment was rarely seen before 2000, with only three patients receiving radiochemotherapy from 1990 to 2000 ($p < 0.001$); the frequency of surgery or radiochemotherapy use is shown in Figure 1. A total of 1,311 patients (35.9%) received adjuvant RT after radical hysterectomy. Patients who were older, of black ethnicity, and with larger tumor size and stage IIA1 disease were more likely to receive definitive radiochemotherapy. A total of 116 pairs were completely matched using PSM. The characteristics of the unmatched and matched populations are listed in Table 1.

The median follow-up for the entire cohort was 103 months. The 5- and 10-year CSS rates were 91.8% and 89.4%, respectively, and the 5- and 10-year OS rates were 87.7% and 81.0%, respectively.

In the univariate analysis of the unmatched population, radical hysterectomy was associated with better CSS and OS. However, the treatment arm was not identified as an independent prognostic factor on multivariate analysis. Age, race/ethnicity, tumor grade, tumor size, FIGO stage, and nodal status were the independent prognostic factors of CSS and OS on multivariate analysis (Tables 2 and 3).

In the matched populations, the local treatment modalities also had no effect on CSS (hazard ratio [HR]: 0.770, 95%

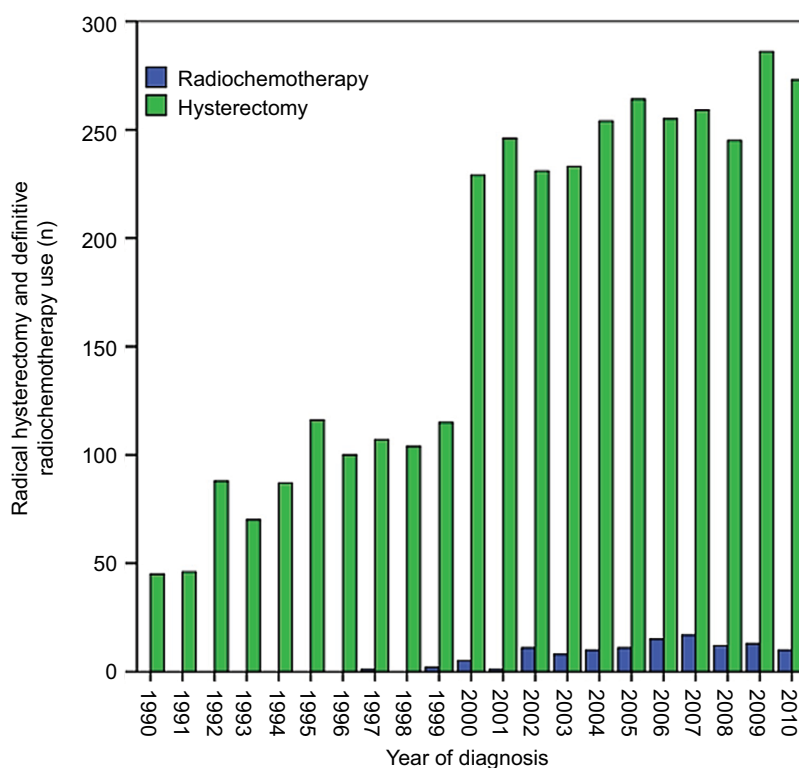


Figure 1 The frequency of radical hysterectomy and definitive radiochemotherapy use (1990–2010).

Table 1 Patient characteristics of unmatched and matched populations

Variables	Unmatched				Matched			
	Patients (N)	Surgery, n (%)	RCT, n (%)	p-value	Patients (N)	Surgery, n (%)	RCT, n (%)	p-value
Age (years)								
<50	2,564	2,504 (68.5)	60 (51.7)	<0.001	116	56 (48.3)	60 (51.7)	0.599
≥50	1,205	1,149 (31.5)	56 (48.3)		116	60 (51.7)	56 (48.3)	
Race/ethnicity								
White	2,926	2,839 (77.7)	87 (75.0)	0.001	171	84 (72.4)	87 (75.0)	0.192
Black	434	410 (11.2)	24 (20.7)		44	20 (17.2)	24 (20.7)	
Others	409	404 (11.1)	5 (4.3)		17	12 (10.3)	5 (4.3)	
Tumor grade								
G1	178	174 (4.8)	4 (3.4)	0.885	11	7 (6.0)	4 (3.4)	0.407
G2	1,722	1,669 (45.7)	53 (45.7)		97	44 (37.9)	53 (45.7)	
G3 and 4	1,869	1,810 (49.5)	59 (50.9)		124	65 (56.0)	59 (50.9)	
Tumor size (mm)								
Mean	22	22	31	<0.001	31	31	31	0.815
FIGO stage								
IB1	3,520	3,428 (93.8)	92 (79.3)	<0.001	183	91 (78.4)	92 (79.3)	0.872
IIA1	249	225 (6.2)	24 (20.7)		49	25 (21.6)	24 (20.7)	
Nodal stage								
Negative	3,099	3,009 (82.4)	90 (77.6)	0.185	177	87 (75.0)	90 (77.6)	0.643
Positive	670	644 (17.6)	26 (22.4)		55	29 (25.0)	26 (22.4)	

Abbreviations: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated; FIGO, International Federation of Gynecology and Obstetrics; RCT, radiochemotherapy.

confidence interval [CI]: 0.427–1.388, $p=0.384$) or OS (HR: 0.732, 95% CI: 0.450–1.189, $p=0.207$) on univariate analysis. The 8-year CSS rates were 82.1% and 76.5% in surgery and radiochemotherapy groups, respectively (log-rank test,

$p=0.382$; Figure 2A). The 8-year OS rates were 74.6% and 67.8% in surgery and radiochemotherapy groups, respectively (log-rank test, $p=0.205$; Figure 2B). Race/ethnicity and tumor size were the independent prognostic factors for survival

Table 2 Univariate prognostic analysis of unmatched and matched populations

Variables	Unmatched				Matched			
	CSS		OS		CSS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)								
<50	1		1		1		1	
≥50	0.967 (0.774–1.209)	0.768	2.125 (1.840–2.453)	<0.001	1.030 (0.574–1.849)	0.920	1.131 (0.702–1.822)	0.613
Race/ethnicity								
White	1		1		1		1	
Black	1.273 (0.947–1.712)	0.110	1.366 (1.114–1.674)	0.003	2.997 (1.626–5.527)	<0.001	2.499 (1.490–4.192)	0.001
Others	0.917 (0.648–1.297)	0.624	0.948 (0.748–1.202)	0.658	0.718 (0.170–3.028)	0.652	0.852 (0.305–2.379)	0.760
Tumor grade								
G1 and 2	1		1		1		1	
G3 and 4	1.640 (1.329–2.024)	<0.001	1.347 (1.165–1.556)	<0.001	2.295 (1.204–4.373)	0.012	1.969 (0.184–3.273)	0.009
Tumor size (mm)	1.065 (1.054–1.076)	<0.001	1.034 (1.027–1.041)	<0.001	1.055 (1.015–1.097)	0.007	1.033 (1.004–1.062)	0.023
FIGO stage								
IBI	1		1		1		1	
IIA1	2.858 (2.154–3.791)	<0.001	2.444 (1.976–3.022)	<0.001	1.056 (0.523–2.133)	0.880	1.440 (0.848–2.447)	0.177
Nodal stage								
Negative	1		1		1		1	
Positive	2.524 (2.032–3.134)	<0.001	1.538 (1.298–1.823)	<0.001	1.418 (0.755–2.666)	0.278	1.127 (0.658–1.932)	0.664
Treatment								
Radiochemotherapy	1		1		1		1	
Hysterectomy	0.390 (0.259–0.585)	<0.001	0.469 (0.336–0.653)	<0.001	0.770 (0.427–1.388)	0.384	0.732 (0.450–1.189)	0.207

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

Table 3 Multivariate prognostic analysis of unmatched and matched populations

Variables	Unmatched				Matched			
	CSS		OS		CSS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)								
<50	–		1		–		–	
≥50	–	–	2.084 (1.800–2.413)	<0.001	–	–	–	–
Race/ethnicity								
White	–		1		1		1	
Black	–	–	1.317 (1.075–1.615)	0.008	2.755 (1.485–5.111)	0.001	2.357 (1.400–3.968)	0.001
Others	–	–	0.812 (0.640–1.031)	0.088	0.716 (0.169–3.034)	0.650	0.834 (0.298–2.337)	0.730
Tumor grade								
G1 and 2	1		1		1		1	
G3 and 4	1.382 (1.118–1.708)	0.003	1.219 (1.054–1.411)	0.008	1.793 (0.925–3.475)	0.084	1.682 (0.999–2.834)	0.050
Tumor size (mm)	1.053 (1.042–1.065)	<0.001	1.028 (1.020–1.035)	<0.001	1.046 (1.006–1.087)	0.023	1.026 (0.998–1.055)	0.073
FIGO stage								
IBI	1		1		–		–	
IIA1	2.063 (1.548–2.749)	<0.001	1.800 (1.449–2.236)	<0.001	–	–	–	–
Nodal stage								
Negative	1		1		–		–	
Positive	1.864 (1.494–2.325)	<0.001	1.375 (1.155–1.636)	<0.001	–	–	–	–
Treatment								
Radiochemotherapy	1		1		–		–	
Hysterectomy	0.693 (0.457–1.050)	0.083	0.799 (0.568–1.124)	0.198	–	–	–	–

Note: “–” indicates no data.

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

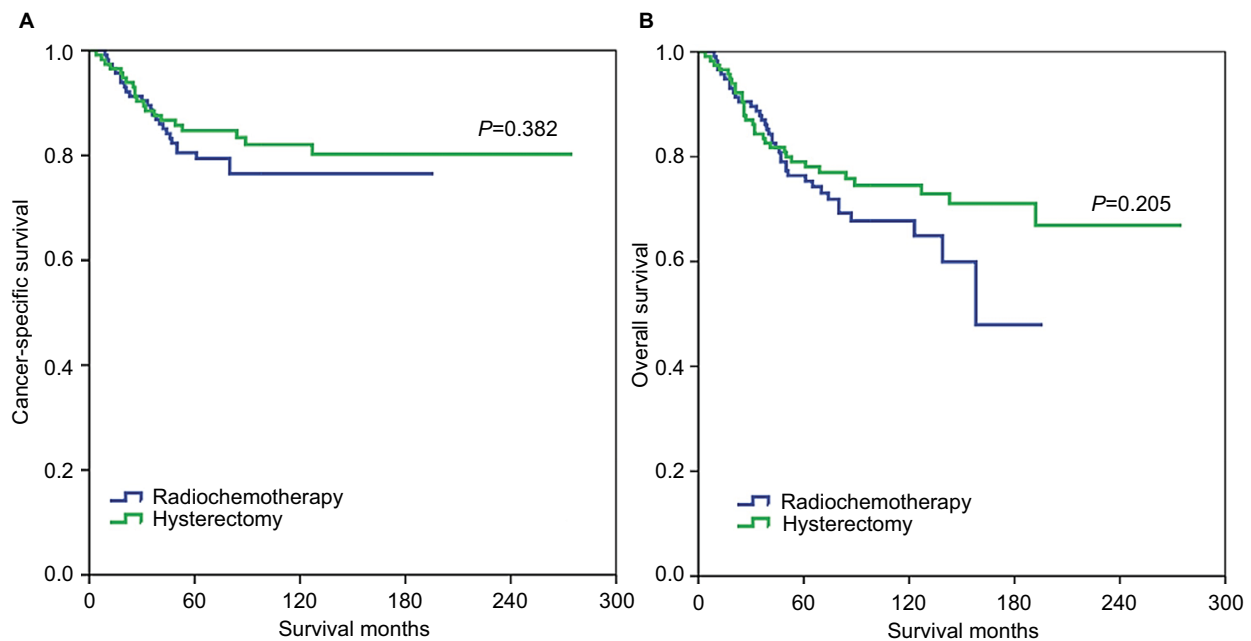


Figure 2 The CSS (A) and OS (B) between patients who underwent radical hysterectomy and definitive radiochemotherapy in the matched population.
Abbreviations: CSS, cancer-specific survival; OS, overall survival.

outcome on multivariate analysis in matched populations (Tables 2 and 3).

Discussion

In this study, we analyzed the effects of different local treatment modalities on the survival of patients with stage IB1 and IIA1 cervical SCC using a population-based database. Our results found that the survival outcomes were similar between radical hysterectomy and definitive radiochemotherapy in both matched and unmatched populations.

The current National Comprehensive Cancer Network Guidelines recommend radical surgery or definitive RT with or without chemotherapy as alternative treatments for stage IB1 and IIA1 CC.⁹ However, surgical treatment is still the main local treatment used for early-stage CC. In our study, the vast majority of patients (96.9%) received surgery-based treatment, and definitive radiochemotherapy was rarely used before 2000, which is related to the inclusion criteria in our study. Since 1999, five randomized trials have confirmed the clinical value of concurrent radiochemotherapy for bulky stage IB CC, high-risk early-stage CC after radical surgery, and locally advanced CC.^{18–22} In patients who received definitive RT, radiochemotherapy (66.7%) was also the main treatment employed for stage IB1 and IIA1 CC in the recent National Cancer Database study and was associated with improved survival compared with definitive RT alone.¹⁴ The introduction of radiochemotherapy in the treatment of stage IB1 and IIA1 CC has gradually increased in recent

years. However, radical surgery is still the most frequent treatment from 2000 to 2010.

To the best of our knowledge, there have been a total of five studies focusing on the survival differences between surgery and definitive RT/radiochemotherapy in patients with early-stage CC in the last two decades,^{10,11,23–25} and the optimal local treatment modality in these patients remains controversial. A randomized study by Landoni et al¹³ found equal survival rates between radical surgery and RT for stage IB–IIA cervical SCC. The 20-year OS rates associated with the two local treatment modalities were comparable in SCC subtype (72% vs 77%, $p=0.280$).²³ A retrospective study from Japan also found no statistically significant difference in survival for stage IA–IIB CC patients who received surgery ($n=115$) and those who received RT ($n=37$; 79.9% vs 82.3%, $p=0.8524$).²⁴ However, a study by Doll et al²⁵ showed that radical hysterectomy ($n=169$) significantly decreased the recurrence rate and improved survival with fewer disease complications compared with RT with or without chemotherapy ($n=29$) in stage IB1 CC. In addition, two previous SEER studies found that surgical treatment was superior to RT for stage IB–IIA CC.^{10,11} In our study, we used PSM to reduce potential selection bias and found that definitive radiochemotherapy showed similar survival to radical hysterectomy for patients with stage IB1 and IIA1 cervical SCC in matched populations. However, radical hysterectomy group has approximately 20%–30% prognosis improvement, compared with radiochemotherapy group. Because of a small number of patients receiving

definitive radiochemotherapy in our study, more prospective studies are needed to confirm our results.

Our results are similar to the randomized study by Landoni et al,^{13,23} but are contrary to the results of the two previous SEER studies.^{10,11} The relevant reasons may be as follows: 1) We only included patients with stage IB1 and IIA1 CC (tumor diameters ≤ 4 cm), whereas patients with tumor diameters >4 cm (stage IB2 and IIA2) were also included in the two previous SEER studies, in which larger tumor size was found to be an adverse prognostic factor.^{10,11} 2) Patients who received RT in our study also received chemotherapy, and several studies have shown that radiochemotherapy is associated with better survival than RT alone.^{14,18} The two previous SEER studies included patients from 1988 to 1995 and 1988 to 2005, respectively, such that most of the patients were not treated in the era of radiochemotherapy, which would have a potential impact on the results. In addition, the CSS and OS in our study were significantly higher than those in the two previous SEER studies. 3) We only included patients with the SCC subtype, whereas adenocarcinoma and adenosquamous carcinoma were also included in the previous SEER studies, and these histological subtypes have different RT sensitivity and chemosensitivity.^{26–30}

Given the similar survival outcomes of patients undergoing radical hysterectomy and definitive radiochemotherapy, the pros and cons associated with each treatment modality play an important role in treatment selection. Surgery allows for the preservation of ovarian function and an accurate pathological assessment of nodal status. RT, on the other hand, is easy to deliver, which is particularly important in elderly patients, obese women, or patients with multiple medical comorbidities or contraindications to surgery. RT also avoids the laparotomy scar and anesthesia risks, and RT-induced iatrogenic mortality is rare. Furthermore, radical hysterectomy and definitive RT differ significantly in their accompanying morbidities and complications. Complications after RT occur later than surgery, although RT-related complications are usually permanent. The introduction of modern RT techniques such as intensity-modulated radiation therapy into clinical practice will yield much better results in terms of survival and morbidity, with significant reductions in chronic gastrointestinal, urinary, and vascular toxicities.³¹

Although 35.9% of patients received postoperative adjuvant RT in our study, approximately two-thirds of patients received adjuvant RT after radical hysterectomy in other studies of patients with IA–IIB stage CC.^{23,24} The incidence of complications in those studies was significantly different between the surgical arm and the RT arm (32% vs 23%, $p=0.006$), especially for leg edema. Leg edema occurred

more often (11.1%) in patients who received adjuvant RT after surgery compared with patients who underwent radical hysterectomy with lymphadenectomy (none) or RT alone (0.6%).²³ Therefore, adjuvant RT may increase the complication rates and decrease the quality of life of patients. Given the disparity in treatment-related morbidity, accurate preoperative assessment of the patients is more important, which could become a useful reference for treatment selection.

Limitations

We admit that our study has several limitations. First, although we used PSM to reduce potential selection bias, the SEER database lacks data on some pathologic variables that are important for CC, including lymphovascular space invasion and depth of tumor invasion. Second, we included a limited number of patients receiving definitive radiochemotherapy. In addition, the sequencing of RT and chemotherapy, the chemotherapy regimen, and the RT techniques and dosages are not recorded in the current SEER database. Moreover, we were unable to obtain the medical comorbidities present in patients before local treatment, which may impact treatment selection. Finally, the patterns of disease recurrence and treatment-related complications are also not available from the SEER database.

Conclusion

This population-based study further confirms that there is no treatment of choice on survival for patients with stage IB1 and IIA1 cervical SCC. The optimal treatment modality for the individual patient should take into consideration clinical factors such as age, body mass index, comorbidities, and sexual function. A prospective randomized trial is warranted to compare the survival and treatment-related complications of these two treatment modalities.

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Disclosure

The authors report no conflicts of interest in this work.

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