Meta-Analysis of Observational Studies in Epidemiology

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Effect of radiotherapy on the survival of cervical cancer patients

An analysis based on SEER database

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Abstract

Cervical cancer is among the most frequent cancer types in women worldwide. Radiotherapy, including external beam radiation and brachytherapy, is one of the commonly used treatment options for cervical cancer. However, the adverse effects of radiation therapy on cervical cancer survival have been poorly investigated with inconclusive results. Therefore, the aim of this study was to determine the suitable radiotherapy modality according to patients' characteristics. A retrospective survival analysis of 44,602 patients was performed using the Surveillance, Epidemiology, and End Results (SEER) database. Multivariate proportional hazard Cox model was used to evaluate the prognostic impact of different radiotherapy modalities, primary surgery, age, TNM stage, and tumor size. Our results indicated that patients without primary surgery, diagnosed at older age (≥45 years' old), at advanced TNM stages (III/IV) or with larger tumor size (≥3 cm) could benefit from radiotherapy. However, radiotherapy was detrimental in patients with primary surgery, diagnosed at younger age (<45 years' old), at earlier TNM stages (I/II) or with smaller tumor size (<3 cm). In addition, external beam radiation was in most cases less effective compared with combined external beam and brachytherapy. These results highlighted the necessity of realizing personalized radiotherapy treatments for patients with cervical cancer.

Abbreviations: CI = confidence interval, CSS = cause-specific survival, FABP4 = fatty acid binding protein 4, HOXB9 = Homeobox 9, HR = hazard ratio, OS = overall survival, ROS = reactive oxygen species, SEER = Surveillance, Epidemiology, and End Results, TRL = tumor-related leukocytosis.

Keywords: cervical cancer, cox model, radiotherapy, SEER database, survival analysis

1. Introduction

Cervical cancer is the fourth most prevalent cancer and the fourth leading cause of cancer death in women worldwide, with an estimated 530,000 new cases and 270,000 deaths every year.[1] Cervical cancer is commonly treated by primary surgery, radiotherapy, and/or chemotherapy. Despite the common use of radiotherapy in clinical practice, its effect and efficiency in the treatment of cervical cancer is controversial. A previous study revealed that surgery and radiotherapy on cervical cancer are associated with similar survival rates in early-stage patients, but radiotherapy has a lower rate of severe morbidity.[2] Single-modality surgery or radiation therapy is preferred to combat cervical cancer, as the combination of these 2 treatments has greater morbidity.[2] Another study showed equivalent efficacy in stage IIA cervical cancer between radical hysterectomy and radiation, and recommends caution in the use of radiotherapy on cervical cancer.[3] Radiotherapy is a risk factor for both cause-specific survival (CSS) and overall survival (OS) in cervical cancer.[4] A recent study suggested that the treatment with primary radiotherapy is associated with worse survival outcomes.[5] Several studies indicated that radiotherapy is associated with an increased risk of a second cancer in cervix and/or other sites.[6–10] Despite the observed detrimental effect of radiotherapy, a significant number of cervical cancer patients undergoes radiotherapy and concurrent surgery.[11] Thus, it is of great importance to determine whether radiotherapy is beneficial or detrimental to cervical cancer patients, and which patients may benefit the most from radiotherapy.

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Therefore, the aim of this study was to explore potential factors that might affect the response to radiotherapy in patients with cervical cancer, providing information for an effective decision-making toward a better therapy. A retrospective survival analysis was performed using the Surveillance, Epidemiology, and End Results (SEER) database. Multivariable Cox analysis showed striking contradictory effects of radiotherapy among patients stratified by a single variable. To be specific, radiotherapy combined with surgery was a risk factor, whereas radiotherapy alone was a beneficial factor. Radiotherapy was a risk factor in patients with TNM stage I/II according to the American Joint Committee on Cancer, whereas it was beneficial in patients with a tumor stage III/IV. Radiotherapy was a risk factor in younger patients (age <45, before menopause), whereas it was beneficial to elder patients (age ≥45, menopause or latter). Furthermore, radiotherapy was a risk factor in patients with smaller tumor size, whereas it was beneficial to patients with a large tumor size. These results indicated that the response to radiotherapy might vary depending on the different clinical characteristics. Thus, the above-mentioned factors should be taken into account before performing radiotherapy to improve the survival of cervical cancer patients. These results might facilitate decision-making changes in clinical practice and might help in assessing an appropriate treatment modality for cervical cancer therapy.

2. Methods

Cervical cancer cases were retrieved from SEER database using SEER*Stat software (Surveillance, Epidemiology, and End Results [SEER] Program [www.seer.cancer.gov] SEER*Stat Database: Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, November 2015 Sub (1973–2013 varying)—Linked To County Attributes—Total US, 1969–2014 Counties National Cancer Institute, DCCPS, Surveillance Research Program, based on the November 2015 submission, seerstat version 8.3.4). The inclusion criteria were the following: diagnosis of cervical cancer between 1998 and 2013 in the November 2015 submission; availability of data regarding age and survival; diagnosis as a single primary cervical cancer; the cause of death was mentioned. This study did not require the patient informed consent, and was conducted according to the institutional and ethical rules concerning research.

The following variables were extracted from the SEER database: follow-up time, vital status at the last follow-up, cause-specific death defined by SEER, age at diagnosis, race, marital status, primary tumor size, histological type, tumor differentiation grade, number of positive lymph nodes, surgery of primary site, regional lymph node surgery, surgery of other regional/distant sites, TNM stage, and radiation. Histological type was transformed into 3 major types based on International Classification of Diseases for Oncology, 3rd Edition (squamous cell carcinoma: 8010,8052–8078,8083–8084; adenocarcinoma: 8140–8147,8255–8384, 8480–8772; other if not squamous cell carcinoma and adenocarcinoma). CSS was defined as the period of time from diagnosis to death caused by cervical cancer. Patients who were alive at the end of the observation period or died from other causes were censored. The "Combine" group in the radiation variable stands for the records of "combination of beam with implants or isotopes." The "No radiation" group was the aggregation of records of "none" and "refused." All the other records were included into the "Other/Unknown" group.

Statistical analysis was performed using R statistical environment (version 3.2.4). Survival analysis was performed by the 'survival' R package. Clinical and demographic statistics were compared by χ^2 tests. Survival curves were plotted by Kaplan–Meier method. Log-rank test was used to determine the variables incorporated into the multivariate model, and the threshold for the P value was set to <.05. The proportional hazard Cox model was used for univariate and multivariate survival analysis. In strata analysis, strata schemes consisting of only 1 level were excluded. Adjusted hazard ratios and their corresponding confidence interval were derived from multivariate Cox model. A 2-tailed P value <.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Surgery is one of the most important treatments for cervical cancer, and may strongly affect the therapeutic response to radiotherapy. Thus, cervical cancer patients diagnosed between 1998 and 2013 were extracted from the SEER database. Clinical records for this period contain information on both radiotherapy and surgery. In total, 44,602 eligible patients were collected with only 1 primary tumor. The statistics of patients receiving different radiotherapy regimens are listed in Table S1, http://links.lww.com/MD/D127. Among them, 20,839 (46.72%) patients did not receive radiotherapy, 11,440 (25.65%) underwent beam radiotherapy, 9711 (21.77%) took combined beam radiotherapy with brachytherapy, and 2612 (5.86%) applied unknown/other radiotherapy. As regard tumor stage, 26,316 (59.00%) patients were in TNM stage I/II, 13,916 (31.20%) were in TNM stage III/IV, and 4370 (9.80%) were in an unknown stage. A large portion of patients (73.1%) who did not receive radiotherapy were in stage I. A total of 25,983 (58.26%) patients were treated with primary surgery, whereas 18,418 (41.29%) were not, and 201 (0.45%) were without treatment information. Approximately, 80.9% patients who did not receive radiotherapy had primary surgery. Among patients who received beam or combined radiotherapy, 58.7% and 65.9% patients did not receive surgery, respectively. As regard the age at diagnosis, 19,477 (43.67%) patients were younger than 45 years, 14,422 (32.33%) were between 45 and 60 years, and 10,703 (24%) were above 60 years. Moreover, 54.3% patients who did not receive radiotherapy were younger than 45 years, and relatively balanced age distributions were observed in beam or combined radiotherapy groups. As regard tumor size, 11,348 (25.44%) patients had a small tumor, 15,364 (34.45%) had a large tumor, and 17,980 (40.31%) had no tumor size records. A large portion of patients who did not receive radiotherapy had a small tumor (41.0%), whereas patients who received beam or combined radiotherapy had a larger tumor (51.4% and 55.3%, respectively).

3.2. Effect of radiotherapy on cervical cancer

To determine the effect of radiotherapy, the proportional hazard Cox model was applied for univariate and multivariate analyses. Several variables were considered, including basic demographic variables (age, sex, race, and marital status), clinical characteristics (tumor size, histological type, differentiation grade, positive lymph node, and TNM stage) and therapies (primary surgery, regional surgery or surgical procedures in another site, radiotherapy). This study was focused on CSS. All these variables were significantly correlated with the CSS of cervical cancer even after controlling other variables (Table 1). As expected, large

Table 1

Univariate and multivariate Cox model for cervical cancer cause-specific survival in full dataset between 1998 and 2013 in SEER database.

Variables	Univariate analysis				Multivariate analysis			
	HR	(95% CI)		P	HR	(95% CI)		P
Age								
<45	Ref				Ref			
[45–60)	1.866	1.783	1.953	<.001	1.179	1.125	1.235	<.001
≥60	3.234	3.091	3.383	<.001	1.558	1.483	1.637	<.001
Race								
White	Ref				Ref			
Black	1.488	1.419	1.560	<.001	1.141	1.087	1.197	<.001
Other	0.968	0.909	1.032	.318	0.897	0.842	0.956	.001
Unknown	0.196	0.131	0.293	<.001	0.254	0.170	0.381	<.001
Marital								
Nevermarried	Ref				Ref			
Usedmarried	1.401	1.338	1.468	<.001	1.075	1.024	1.130	.004
Married	0.711	0.679	0.744	<.001	0.847	0.809	0.888	<.001
Unknown	0.772	0.707	0.843	<.001	0.819	0.748	0.896	<.001
Tumor size								
<3 cm	Ref				Ref			
≥3 cm	7.146	6.617	7.718	<.001	2.001	1.841	2.175	<.001
Unknown	5.803	5.373	6.267	<.001	2.028	1.868	2.202	<.001
Histological type								
Squamous cell carcinoma	Ref				Ref			
Adenocarcinoma	0.807	0.772	0.844	<.001	1.276	1.218	1.336	<.001
Other or unknown	2.271	2.119	2.434	<.001	1.900	1.763	2.047	<.001
Grade								
I	Ref				Ref			
II	2.435	2.203	2.692	<.001	1.516	1.369	1.678	<.001
III	4.128	3.741	4.554	<.001	1.946	1.760	2.151	<.001
IV	5.331	4.675	6.079	<.001	2.022	1.766	2.314	<.001
Unknown	2.295	2.076	2.536	<.001	1.304	1.178	1.445	<.001
Positive nodes								
0 node	Ref				Ref			
1∼3 nodes	4.180	3.822	4.571	<.001	1.011	0.916	1.116	.824
≥4 modes	6.907	6.167	7.736	<.001	1.209	1.072	1.365	.002
Unknown	5.251	4.930	5.592	<.001	1.255	1.114	1.414	<.001
Primary surgery								
No	Ref				Ref			
Yes	0.174	0.167	0.182	<.001	0.497	0.470	0.525	<.001
Unknown	0.733	0.584	0.920	.007	1.034	0.782	1.368	.812
Regional node surgery								
No	Ref				Ref			
Yes	0.329	0.314	0.344	<.001	0.767	0.684	0.860	<.001
Unknown	1.135	0.994	1.295	.061	1.074	0.923	1.249	.356
Other site surgery								
No	Ref				Ref			
Yes	1.312	1.195	1.440	<.001	1.119	1.015	1.234	.024
Unknown	1.330	1.086	1.630	.006	1.136	0.875	1.476	.338
Radiotherapy								
No	Ref				Ref			
Beam	3.668	3.506	3.838	<.001	0.909	0.863	0.959	<.001
Combine	2.250	2.140	2.365	<.001	0.590	0.556	0.626	<.001
Other or unknown	2.421	2.239	2.618	<.001	0.789	0.727	0.857	<.001
TNM stage								
I	Ref				Ref			
II	4.631	4.312	4.974	<.001	2.320	2.138	2.517	<.001
III	7.725	7.265	8.213	<.001	4.453	4.126	4.806	<.001
IV	25.015	23.552	26.569	<.001	10.628	9.868	11.446	<.001
Unknown	5.660	5.263	6.087	<.001	2.676	2.468	2.902	<.001

CI = confidence interval, HR = hazard ratio, SEER = Surveillance, Epidemiology, and End Results.

tumor size (hazard ratio [HR]: 2.028, 95% confidence interval (CI): 1.841–2.175; $P < .001$) and higher TNM stage (stage II, HR: 2.320, 95% CI: 2.138–2.517; stage III, HR: 4.453, 95% CI: 4.126–4. 806; and stage IV, HR: 10.628, 95% CI: 9.868–11.446; $P < .001$) were strong risk factors. Elderly patients were more vulnerable to cervical cancer (45∼60 years, HR: 1.179, 95% CI: 1.125–1.235; >60 years, HR: 1.558, 95% CI: 1.483–1.637; $P < .001$). According to the results, primary surgery was

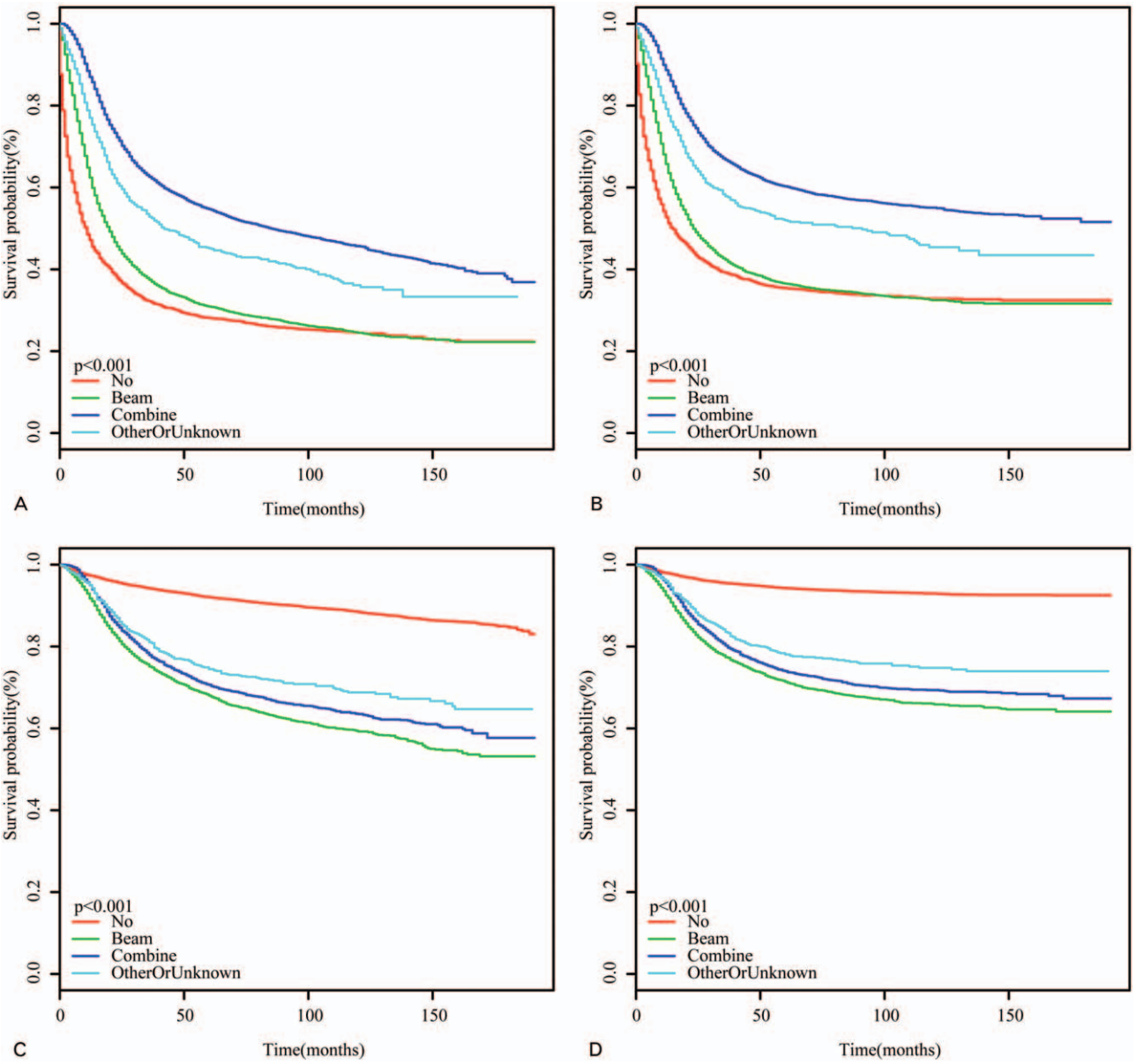

Figure 1. Survival curves in cervical cancer patients according to radiotherapy stratified by primary surgery. (A) Overall survival of no primary surgery group, $\chi^2 = 1577.663$, $P < .001$. (B) Cause-specific survival of no primary surgery group, $\chi^2 = 1364.916$, $P < .001$. (C) Overall survival of primary surgery group, $\chi^2 = 2184.722$, $P < .001$. (D) Cause-specific survival of primary surgery group, $\chi^2 = 2234.601$, $P < .001$.

beneficial for patients (HR: 0.497, 95% CI: 0.470–0.525; $P < .001$). Regional lymph node excision (HR: 0.767, 95% CI: 0.684–0.860; $P < .001$) was also beneficial, whereas taken other site surgery in addition to primary and/or regional lymph node surgery (HR: 1.119, 95% CI: 1.015–1.234; $P = .024$) was a risk factor. Consistent with previous reports, patients receiving radiotherapy exhibited lower OS and CSS (Fig. S1, http://links.lww.com/MD/D127). However, when other variables were included, the 2 radiotherapy modalities were beneficial (beam, HR: 0.909, 95% CI: 0.862–0.959; combined radiotherapy, HR: 0.590, 95% CI: 0.556–0.626; $P < .001$). To further determine whether radiotherapy has unbalanced effect, patients were stratified by different variables.

3.3. Subgroup analysis according to whether adopted primary surgery

Surgery is the recommended treatment strategy for cervical cancer patients, especially those with early-stage cancer.[1] Primary surgery was one of the beneficial variables that had a great effect on CSS. Thus, patients were stratified into "no primary surgery" and "adopted primary surgery" groups. In the primary surgery group, radiotherapy resulted in a lower OS and CSS. In no primary surgery group, combined beam with implants or isotopes resulted in the highest OS and CSS (Fig. 1). The effect of beam radiation on the survival was the worst. As shown in Table 2, when other variables were included, any type of radiotherapy was beneficial to patients with no primary surgery

Table 2

Univariate and multivariate Cox model for evaluating effect of radiotherapy on cervical cancer cause-specific survival in full dataset and subsets stratified by primary surgery, TNM stage, age, and tumor size.

Dataset	Group		Univariate				Multivariate			
		Cases	HR	95% CI		P	HR	95% CI		P
Full	No	20,839	Ref				Ref			
	Beam	11,440	3.668	3.506	3.838	<.001	0.909	0.863	0.959	<.001
	Combine	9711	2.250	2.140	2.365	<.001	0.590	0.556	0.626	<.001
	Other or unknown	2612	2.421	2.239	2.618	<.001	0.789	0.727	0.857	<.001
NoPriSurg	No	3920	Ref				Ref			
	Beam	6712	0.780	0.739	0.823	<.001	0.624	0.588	0.661	<.001
	Combine	6403	0.366	0.345	0.389	<.001	0.376	0.352	0.402	<.001
	Other or unknown	1383	0.492	0.448	0.541	<.001	0.518	0.470	0.572	<.001
PriSurg	No	16,868	Ref				Ref			
	Beam	4710	5.583	5.130	6.076	<.001	1.768	1.598	1.956	<.001
	Combine	3265	4.798	4.365	5.273	<.001	1.493	1.337	1.666	<.001
	Other or unknown	1140	3.872	3.337	4.493	<.001	1.459	1.248	1.706	<.001
StageI/II	No	15,726	Ref				Ref			
	Beam	4393	6.841	6.205	7.543	<.001	2.436	2.163	2.743	<.001
	Combine	4889	6.022	5.468	6.632	<.001	1.770	1.564	2.003	<.001
	Other or unknown	1318	4.938	4.246	5.744	<.001	1.929	1.638	2.273	<.001
StageIII/IV	No	2579	Ref				Ref			
	Beam	6200	0.498	0.470	0.527	<.001	0.562	0.530	0.597	<.001
	Combine	4167	0.295	0.276	0.316	<.001	0.342	0.319	0.368	<.001
	Other or unknown	970	0.393	0.354	0.436	<.001	0.467	0.420	0.519	<.001
Age <45	No	11,325	Ref				Ref			
	Beam	3778	8.144	7.427	8.929	<.001	1.954	1.740	2.195	<.001
	Combine	3435	5.910	5.364	6.512	<.001	1.274	1.125	1.443	<.001
	Other or unknown	939	5.295	4.568	6.138	<.001	1.620	1.378	1.905	<.001
Age ≥45	No	9514	Ref				Ref			
	Beam	7662	2.082	1.976	2.193	<.001	0.716	0.675	0.759	<.001
	Combine	6276	1.183	1.115	1.255	<.001	0.451	0.421	0.483	<.001
	Other or unknown	1673	1.399	1.275	1.534	<.001	0.619	0.562	0.682	<.001
Tumor size <3 cm	No	8540	Ref				Ref			
	Beam	1436	6.767	5.715	8.012	<.001	1.899	1.546	2.333	<.001
	Combine	969	5.144	4.209	6.288	<.001	1.259	0.984	1.610	.068
	Other or unknown	403	4.228	3.110	5.746	<.001	1.541	1.108	2.142	.010
Tumor size ≥3 cm	No	3028	Ref				Ref			
	Beam	5877	1.348	1.252	1.451	<.001	0.716	0.662	0.776	<.001
	Combine	5372	0.852	0.788	0.922	<.001	0.464	0.425	0.506	<.001
	Other or unknown	1087	0.983	0.870	1.111	.782	0.572	0.504	0.649	<.001

CI = confidence interval, HR = hazard ratio, NoPriSurg = patients without primary surgery, PriSurg = patients underwent primary surgery.

(beam, HR: 0.624, 95% CI: 0.588–0.661; combined radiotherapy, HR: 0.376, 95% CI: 0.352–0.402; $P < .001$), but was detrimental for patients who were subjected to primary surgery (beam, HR: 1.768, 95% CI: 0.598–1.956; combined radiotherapy, HR: 1.493, 95% CI: 1.337–1.666; $P < .001$).

3.4. Subgroup analysis according to TNM stage

Tumor stage is one of the main factors that affect cancer survival. Cancer cells from cervical cancer patients at an advanced stage exhibited higher rate of DNA synthesis and more rapid cell proliferation.[12] Radiotherapy is particularly effective on cancer cells during DNA synthesis and active proliferation, owing to the DNA damage effects of radiotherapy. Thus, tumor stage may have a significant effect on response after radiotherapy. Patients were stratified into 2 groups, such as relative early stages (stage I and II) or late stages (stage III and IV), to investigate the efficiency of radiotherapy. Figure 2 shows that radiotherapy on patients diagnosed at early stages resulted in a lower OS and CSS. Radiotherapy on late-stage patients resulted in an improved OS and CSS. After including other variables, radiotherapy on patients diagnosed at stage I and II was a risk factor (beam, HR: 2.436, 95% CI: 2.163–2.743; combined radiotherapy, HR: 1.770, 95% CI: 1.564–2.003; $P < .001$), whereas radiotherapy on patients diagnosed at stage III and IV was a beneficial factor (beam, HR: 0.562, 95% CI: 0.530–0.597; combined radiotherapy, HR: 0.342, 95% CI: 0.319–0.368; $P < .001$) (Table 2). These results highlighted the importance of assigning different radiotherapy treatments or evaluating the use of radiotherapy on cervical cancer patients based on tumor stages.

3.5. Subgroup analysis according to age

Women inevitably start menopause between age 45 and 55. During this time, most women experience mental and physical changes.[13,14] Such changes may have potent effect on the response to cancer treatment and survival. Therefore, patients were stratified into 2 groups: younger than 45 years (before menopause) and older than 45 years (menopause or after menopause). Patients diagnosed before menopause had relatively

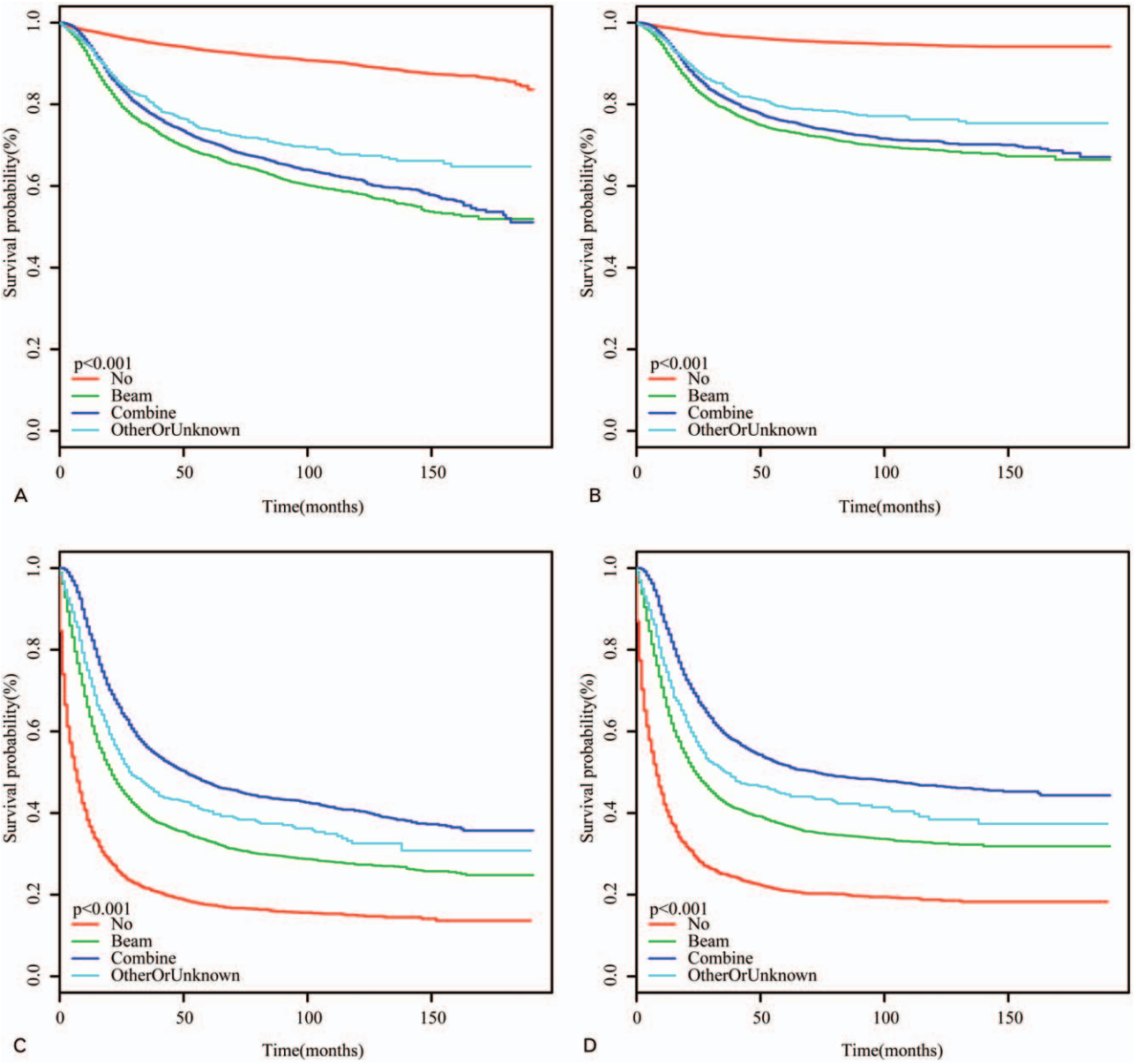

Figure 2. Survival curves in cervical cancer patients according to radiotherapy stratified by TNM stage. (A) Overall survival of stage I/II group, $\chi^2 = 2590.879$, $P < .001$. (B) Cause-specific survival of stage I/II group, $\chi^2 = 2296.589$, $P < .001$. (C) Overall survival of stage III/IV group, $\chi^2 = 1573.882$, $P < .001$. (D) Cause-specific survival of stage III/IV group, $\chi^2 = 1431.397$, $P < .001$.

higher OS and CSS compared to those diagnosed at or after menopause. Nevertheless, radiotherapy treatment led to lower OS and CSS in both groups (Fig. 3). However, the multivariate Cox model revealed that radiotherapy had an adverse effect on cervical cancer patients diagnosed before menopause (beam, HR: 1.954, 95% CI: 1.740–2.195; combined radiotherapy, HR: 1.274, 95% CI: 1.125–1.443; $P < .001$), whereas it was beneficial to patients who were diagnosed at or post-menopause (beam, HR: 0.716, 95% CI: 0.675–0.759; combined radiotherapy, HR: 0.451, 95% CI: 0.421–0.483; $P < .001$) (Table 2).

3.6. Subgroup analysis according to tumor size

In a previous study, tumor size appeared as an independent factor for cervical cancer survival.[15] Then, the effect of radiotherapy on cervical cancer patients with different tumor sizes was evaluated. Patients without radiotherapy and with a tumor size <3 cm in its largest dimension showed a higher survival rate (Fig. 4). The multivariate Cox model revealed that radiotherapy on patients who had smaller tumors was a detrimental factor (beam, HR: 1.899, 95% CI: 1.546–2.333; $P < .001$; combined radiotherapy, HR: 1.259, 95% CI: 1.108–1.610; $P = .068$), whereas it was beneficial to patients who had larger tumors (beam, HR: 0.716, 95% CI: 0.662–0.776; combined radiotherapy, HR: 0.464, 95% CI: 0.425–0.506; $P < .001$) (Table 2).

4. Discussion

Radiotherapy is one of the most common treatment options for cervical cancer. It is usually applied alone on tumors or in

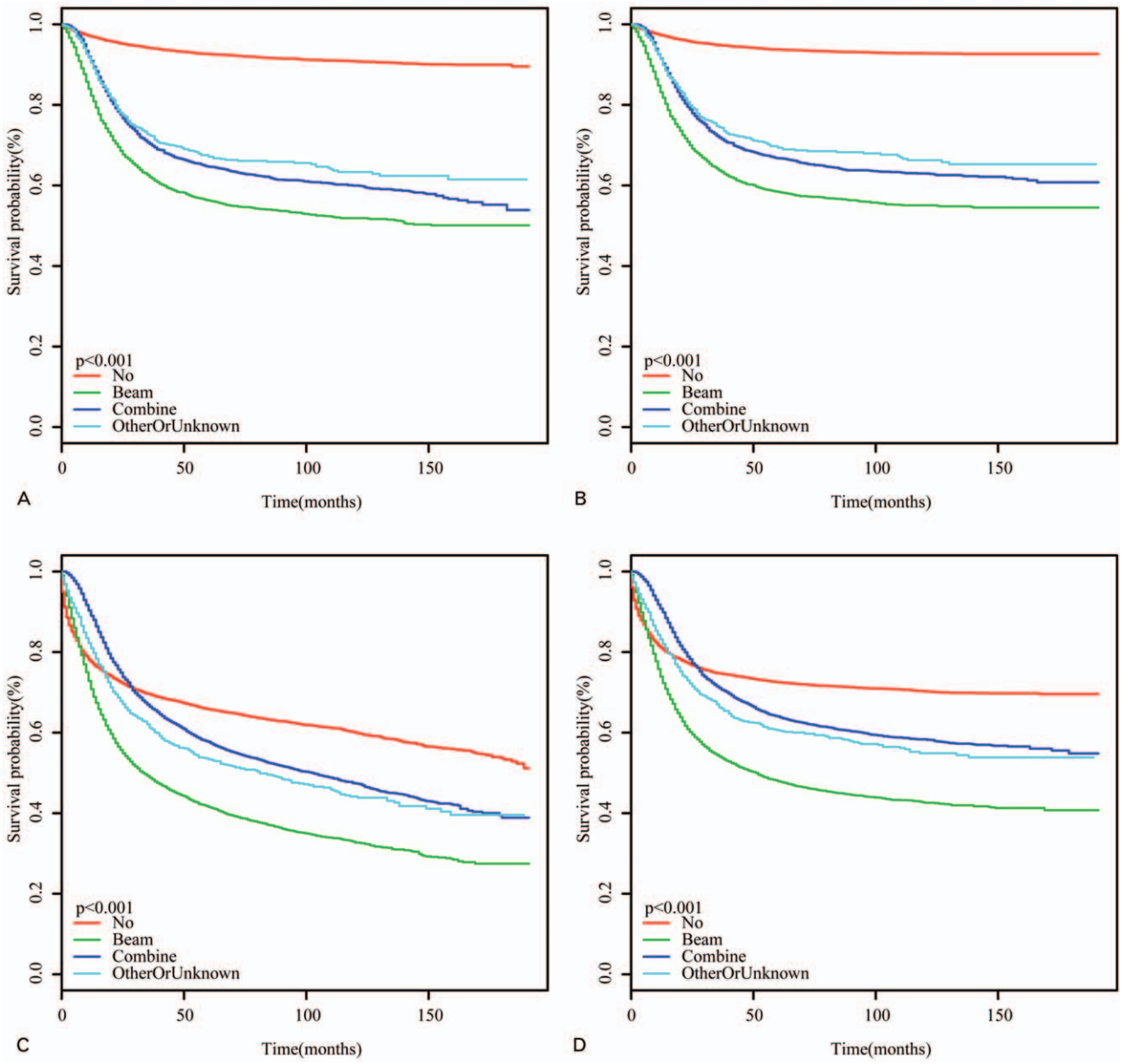

Figure 3. Survival curves in cervical cancer patients according to radiotherapy stratified by age at diagnosis. (A) Overall survival of younger group, $\chi^2 = 2867.453$, $P < .001$. (B) Cause-specific survival of younger group, $\chi^2 = 2815.305$, $P < .001$. (C) Overall survival of older group, $\chi^2 = 920.560$, $P < .001$. (D) Cause-specific survival of older group, $\chi^2 = 897.282$, $P < .001$.

combination with surgery and/or chemotherapy. Many studies evaluating its detrimental effect on patients including an increased risk of secondary cancer and lower survival rate have been published.[5–9] Some studies suggested that radiotherapy should not be combined with surgery in locally advanced cervical cancer treatment because combination of the 2 modalities may be harmful to cervical cancer patients.[2,16] Our study indicated that postoperative radiotherapy should not be performed in patients after surgery. According to our results, beam radiation confers less benefit to the survival of cervical cancer patients compared with combined beam with brachytherapy. This is consistent with a recent study which suggested that combined brachytherapy with external beam radiation was better than external beam radiation alone in the treatment of cervical cancer.[17] However, brachytherapy is a demanding approach that requires significant resources and infrastructure, skilled radiologists, and complicated procedures, and is unavailable in some resource-limited countries. The use of brachytherapy declined significantly in recent years.[3,18] In this case, further investigation is required to evaluate the effect of radiotherapy in cervical cancer, to better understand the disparity of response to radiotherapy among patients with different demographic and pathological characteristics.

TNM stage and tumor size have long be recognized as independent prognostic factors for cervical cancer survival. To our knowledge, the different response to radiotherapy is not well studied in cervical cancer. In this study, a differential response to radiotherapy was found among different patient groups stratified

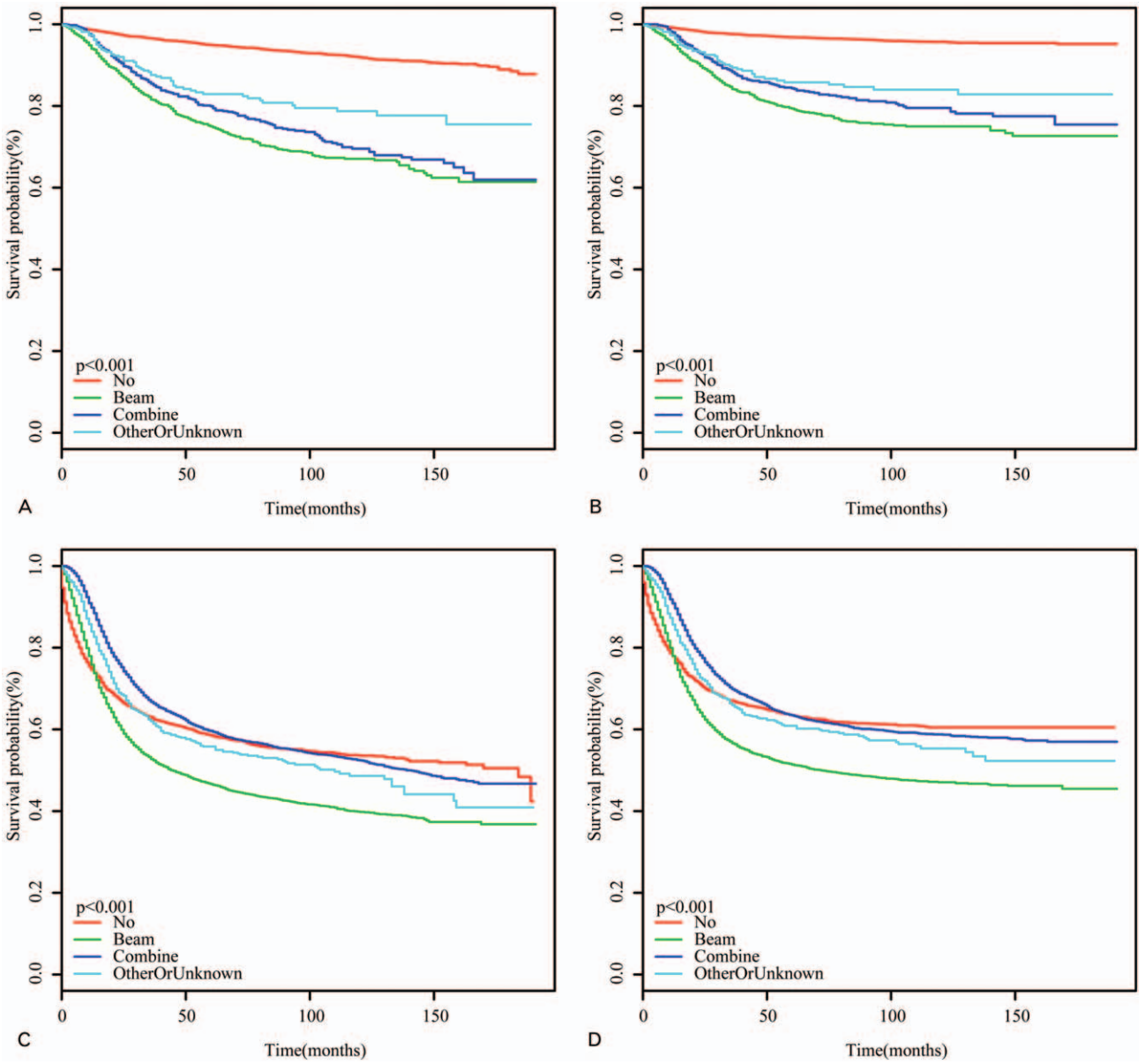

Figure 4. Survival curves in cervical cancer patients according to radiotherapy stratified by tumor size. (A) Overall survival of smaller tumor group, $\chi^2 = 774.510$, $P < .001$. (B) Cause-specific survival of smaller tumor group, $\chi^2 = 717.422$, $P < .001$. (C) Overall survival of large tumor group, $\chi^2 = 253.402$, $P < .001$. (D) Cause-specific survival of large tumor group, $\chi^2 = 229.275$, $P < .001$.

by TNM stages and tumor size. Radiotherapy is widely used in treatment of locally advanced cervical cancer. Radiotherapy targeting proliferating cells has high efficiency to kill tumor cells that usually proliferate rapidly. An early study indicated that tumor size was positively correlated with tumor proliferation in breast cancer.[19] This may partially explain why patients with larger tumor and advanced stage response better to radiotherapy. Early-stage tumor has a high DNA damage response and is more resistant to radiotherapy.[20] We reanalyzed the expression data of primary tumor samples from The Cancer Genome Atlas cervical cancer cohort (data not shown). Among the differentially expressed genes, *APOBEC1*, fatty acid binding protein 4 (*FABP4*), and homeobox 9 (*HOXB9*) were downregulated in stage III/IV tumor samples compared with stage I/II samples. By stabilizing cyclooxygenase-2 messenger RNA, *APOBEC1* can exert radioprotective effects on intestinal stem cells.[21] *HOXB9* expression can lead to hyperactivation of ataxia telangiectasia mutated gene, rapid accumulation of phosphorylated histone 2AX and p53 binding protein 1 at double-stranded DNA breaks, and enhance DNA repair upon radiation in breast cancer.[22] Lower expression of the 2 genes may be associated with relatively lower radioprotection and DNA-damage response in later tumor stage. *FABP4* involved in lipid uptake and metabolism can promote triacylglycerol upregulation in serum and lipid accumulation. *FABP4* is induced by radiation, leading to lipid accumulation in dendritic cells. Such effect impairs dendritic cells function in immune response and promotes the survival of cancer cells.[23] The lower expression of *FABP4* in stage III/IV tumor

samples may result in radiation-induced lower inhibitory effect on dendritic cells, and a better immune response to radiotherapy. The better response to radiotherapy in later stage cervical cancer patients may be because of a better immune response of patients and less effective DNA-damage response in cancer cells.

Age at diagnosis seems to be an important variable for the prognosis of cervical cancer after radiotherapy. In this study, radiotherapy was unfavorable in young patients. A recent study in Japanese also reported worse survival in young patients after radiation-based treatment.[24] Women encounter major physiological and psychological changes between age 45 and 55 when menopause occurs. Major changes include the lack of sex hormones such as estrogen, and physical conditions, such as metabolic changes, a high risk of cardiovascular disease and bone fractures.[25] Energy accessibility is crucial for cancer cell survival. The disruption of the energy regulation program is considered as a hallmark of cancer.[26] Estrogen can significantly regulate energy intake and expenditure by directly or indirectly controlling the expression of enzymes involved in energy regulation, such as hexokinases.[25,27] An early report suggests that expression of estrogen receptor is a prognostic factor in cervical cancer.[28] Recent findings also suggest that estrogens can promote mitochondrial reactive oxygen species (ROS) production and enhance detoxifying enzymes and antioxidants simultaneously in tumor cells.[29] Consequently, estrogen increase ROS tolerance by cancer cells, thus promoting their survival and metastatic potential. Patients at menopause or postmenopause may be benefit from lower estrogen level because of the lower resistance to ROS by cancer cells, attenuating their metastatic potential. In addition, several studies reported that tumor-related leukocytosis (TRL) is associated with young age and large tumor size in cervical cancer[30–32]. TRL-positive tumor shows increased expression of granulocyte colony-stimulating factor, which contributes to myeloid-derived suppressor cell expansion and radio-resistance.[30] Thus, estrogen expression and TRL infiltration may explain why young patients poorly respond to radiotherapy in cervical cancer.

Some limitations should be acknowledged in this study. First, information on chemotherapy was not included because of limitation of SEER records. Second, some potential confounding factors, such as time of completion of radiotherapy and dose used, were not included. Third, the study was limited to the US population. It might be not appropriate to generalize the results to the global population. Thus, a well-designed prospective study and confirmation on different populations might result in the confirmation of the present results.

5. Conclusion

Our results reveal that cervical cancer patients exhibit different responses to radiotherapy. The survival rates of patients receiving both surgery and radiotherapy are relatively low. Many clinical features should be considered when applying radiotherapy to cervical cancer patients, including age, tumor size, and TNM stage. In addition, external beam radiation alone is less effective than combined radiotherapy in cervical cancer treatment.

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