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, HOBX9 = 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.[3] 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.[4] 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 undergo 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.
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 later). 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; adenosquamous carcinoma: 8140–8147,8255–8384,8480–8772; other if not squamous cell carcinoma and adenosquamous carcinoma). 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 χ² 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 <0.05. 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 <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Survival 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 (73.1%) 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
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

| 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        |   | 1.179      | 1.235 | 1.235 | <.001 |
| 45–60    | 1.866      | 1.783 | 1.953 | <.001 |
| ≥60      | 3.234      | 3.001 | 3.383 | <.001 |
| Race     |            |   |            |   |
| White    | Ref        |   | 1.141      | 1.087 | 1.197 | <.001 |
| Black    | 1.488      | 1.419 | 1.560 | <.001 |
| Other    | 0.968      | 0.909 | 1.032 | .318 |
| Unknown  | 0.196      | 0.131 | 0.293 | <.001 |
| Marital  |            |   |            |   |
| Nevermarried | Ref   |   | 1.075      | 1.024 | 1.130 | .044 |
| Usedmarried | 1.401 | 1.338 | 1.468 | <.001 |
| Married  | 0.711      | 0.679 | 0.744 | <.001 |
| Unknown  | 0.772      | 0.707 | 0.843 | <.001 |
| Tumor size|            |   |            |   |
| <3 cm    | Ref        |   | 2.001      | 1.841 | 2.175 | <.001 |
| ≥3 cm    | 7.146      | 6.617 | 7.718 | <.001 |
| Unknown  | 5.803      | 5.373 | 6.267 | <.001 |
| Histological type |            |   |            |   |
| Squamous cell carcinoma | Ref |   | 1.276      | 1.218 | 1.336 | <.001 |
| Adenocarcinoma | 0.807 | 0.772 | 0.844 | <.001 |
| Other or unknown | 2.271 | 2.119 | 2.434 | <.001 |
| Grade    |            |   |            |   |
| I        | Ref        |   | 1.516      | 1.369 | 1.678 | <.001 |
| II       | 2.435      | 2.203 | 2.692 | <.001 |
| III      | 4.128      | 3.741 | 4.554 | <.001 |
| IV       | 5.331      | 4.675 | 6.079 | <.001 |
| Unknown  | 2.295      | 2.076 | 2.536 | <.001 |
| Positive nodes |            |   |            |   |
| 0 node   | Ref        |   | 1.011      | 0.916 | 1.116 | .244 |
| 1–3 nodes | 4.180 | 3.822 | 4.571 | <.001 |
| ≥4 modes | 6.907      | 6.167 | 7.738 | <.001 |
| Unknown  | 5.251      | 4.930 | 5.592 | <.001 |
| Primary surgery |            |   |            |   |
| No       | Ref        |   | 1.209      | 1.072 | 1.365 | .002 |
| Yes      | 0.174      | 0.167 | 0.182 | <.001 |
| Unknown  | 0.733      | 0.584 | 0.920 | .007 |
| Regional node surgery |            |   |            |   |
| No       | Ref        |   | 1.034      | 0.782 | 1.368 | .123 |
| Yes      | 0.174      | 0.167 | 0.182 | <.001 |
| Unknown  | 0.733      | 0.584 | 0.920 | .007 |
| Other site surgery |            |   |            |   |
| No       | Ref        |   | 1.074      | 0.923 | 1.249 | .356 |
| Yes      | 1.312      | 1.195 | 1.440 | <.001 |
| Unknown  | 1.330      | 1.086 | 1.630 | .006 |
| Radiotherapy |            |   |            |   |
| No       | Ref        |   | 1.136      | 0.875 | 1.476 | .338 |
| Beam     | 3.668      | 3.506 | 3.838 | <.001 |
| Combine  | 2.250      | 2.140 | 2.365 | <.001 |
| Other or unknown | 2.421 | 2.239 | 2.618 | <.001 |
| TNM stage| I          | Ref | 2.520      | 2.138 | 2.517 | <.001 |
| II       | 4.631      | 4.312 | 4.974 | <.001 |
| III      | 7.725      | 7.265 | 8.213 | <.001 |
| IV       | 25.015     | 23.552 | 26.509 | <.001 |
| Unknown  | 5.660      | 5.263 | 6.087 | <.001 |

CI = confidence interval, HR = hazard ratio, SEER = Surveillance, Epidemiology, and End Results.
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.\(^\text{11}\) 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.
Tumor size ≥ and II) or late stages (stage III and IV), to investigate the effects of radiotherapy. Thus, tumor stage may have a significant influence 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. After including other variables, radiotherapy on patients diagnosed at stage I and II was a risk factor (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 stage I and II or 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: 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; \( P < .001 \)).

3.5. 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...
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...
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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[117]} 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.\textsuperscript{[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 been 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 3. Survival curves in cervical cancer patients according to radiotherapy stratified by age at diagnosis. (A) Overall survival of younger group, $\chi^2=2867.493$, $P<.001$. (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, $\chi^2=897.282$, $P<.001$. 

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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 respond 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 H2AX 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

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**Figure 4.** Survival curves in cervical cancer patients according to radiotherapy stratified by tumor size. (A) Overall survival of smaller tumor group, χ² = 774.510, P < .001. (B) Cause-specific survival of smaller tumor group, χ² = 717.422, P < .001. (C) Overall survival of large tumor group, χ² = 253.402, P < .001. (D) Cause-specific survival of large tumor group, χ² = 229.275, P < .001.
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. 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. Energy accessibility is crucial for cancer cell survival. The disruption of the energy regulation program is considered as a hallmark of cancer. Estrogen can significantly regulate energy intake and expenditure by directly or indirectly controlling the expression of enzymes involved in energy regulation, such as hexokinases. An early report suggests that expression of estrogen receptor is a prognostic factor in cervical cancer. Recent findings also suggest that estrogens can promote mitochondrial reactive oxygen species (ROS) production and enhance detoxifying enzymes and antioxidants simultaneously in tumor cells. Consequently, estrogen increase ROS tolerance by cancer cells, thus promoting their survival and metastatic potential. Patients at menopause or post-menopause 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. TRL-positive tumor shows increased expression of granulocyte colony-stimulating factor, which contributes to myeloid-derived suppressor cell expansion and radio-resistance. 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 chemotheraphy 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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