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ORIGINAL RESEARCH

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Effect of primary radiotherapy on the survival rate of stage IVB cervical cancer patients and factors related to their survival: a real-world study based on SEER database

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Abstract

This study aimed to investigate the survival and influence factors of radiation therapy on primary tumors in patients with stage IVB cervical cancer. The data of 3129 stage IVB cervical cancer patients diagnosed from 2000 to 2018 in the Surveillance, Epidemiology and End Results (SEER) database were retrieved, and the propensity score matching (PSM) was used to balance variate and eliminate selection bias. The Kaplan-Meier (K-M) method was used to plot surviving profile. Univariate and multivariate analyses were used to estimate influencing factors of surviving time of stage IVB cervical cancer. After screening the SEER database, 3129 stage IVB cervical cancer patients were selected, including 2166 cases (69.2%) cases with and 963 without primary radiotherapy. PSM analysis identified 860 pairs of patients were one-to-one matched and further enrolled of radiotherapy part as well as non-radiotherapy part (control group) respectively for survival analysis. The K-M curve was compared among the two groups, and radiation therapy was found to be associated with longer survival before (Hazard ratio (HR) = 0.54,95% confidence interval (95% CI): 0.50–0.59, $p < 0.001$) and after (HR = 0.71, 95% CI: 0.64–0.79, $p < 0.001$) PSM. Multivariate Cox analysis confirmed that patients treated with radiotherapy, chemotherapy and local surgery had greater survival benefits, while high-grade tumor lesions, bone metastases, liver metastases and lung metastases were associated with significantly increased mortality. The survival rates varied among different races and were statistically different ($p < 0.05$). Conclusion: Primary radiotherapy could prolong the overall survival (OS) of stage IVB cervical cancer patients.

Keywords

Radiotherapy; Cervical cancer; Survival rate; Stage IVB cervical cancer

1. Introduction

The human papillomavirus vaccination and cervical cancer screening have helped prevent cervical cancer and increased its early detection rates, which have led to a significant reduction in the occurrence of cervical cancer and its precancerous lesions [1, 2]. However, in less developed nations, cervical cancer is still the most frequent malignancy of women's genital system [3, 4]. It is ranked second as the most malignant tumor of the female reproductive system worldwide and seriously threatens women's health. The staging of cervical cancer in this study is based on the 8th edition of the American Joint Council of Cancer (AJCC) and the International Federation of Women and Gynaecologists (FIGO) staging criteria. Stage IVB uterine cervical cancer includes patients with distant systemic metastasis and far-end lymph node metastasis and excludes those with metastasized retroperitoneal abdominal paraaortic lymph nodes. Approximately 13% of cervical cancer patients present with stage IV at the time of their diagnosis [5], and about 3% have already advanced to stage IVB cervical cancer (FIGO criteria) [6]. The prognosis of stage IVB cervical cancer patients is dismal and requires more effort to improve survival and quality of life.

Currently, there is no standardized treatment for metastatic cervical cancer due to different sites of metastasis and physical conditions of the patients, leading to poor survival ranging between 8 and 13 months [7]. Although cervical cancer is very sensitive to the chemotherapy, recurrence of advanced cervical cancer is almost inevitable. Up to 70% of the patients with lymph node metastasis suffer from local recurrence [8], among which pelvic metastasis is the main cause of recurrence. Presently, systemic chemotherapy, the main treatment for these patients, is often supplemented with radiotherapy [9, 10]. However, few studies have explored the related factors and the effects of radiotherapy on the primary tumor [11, 12].

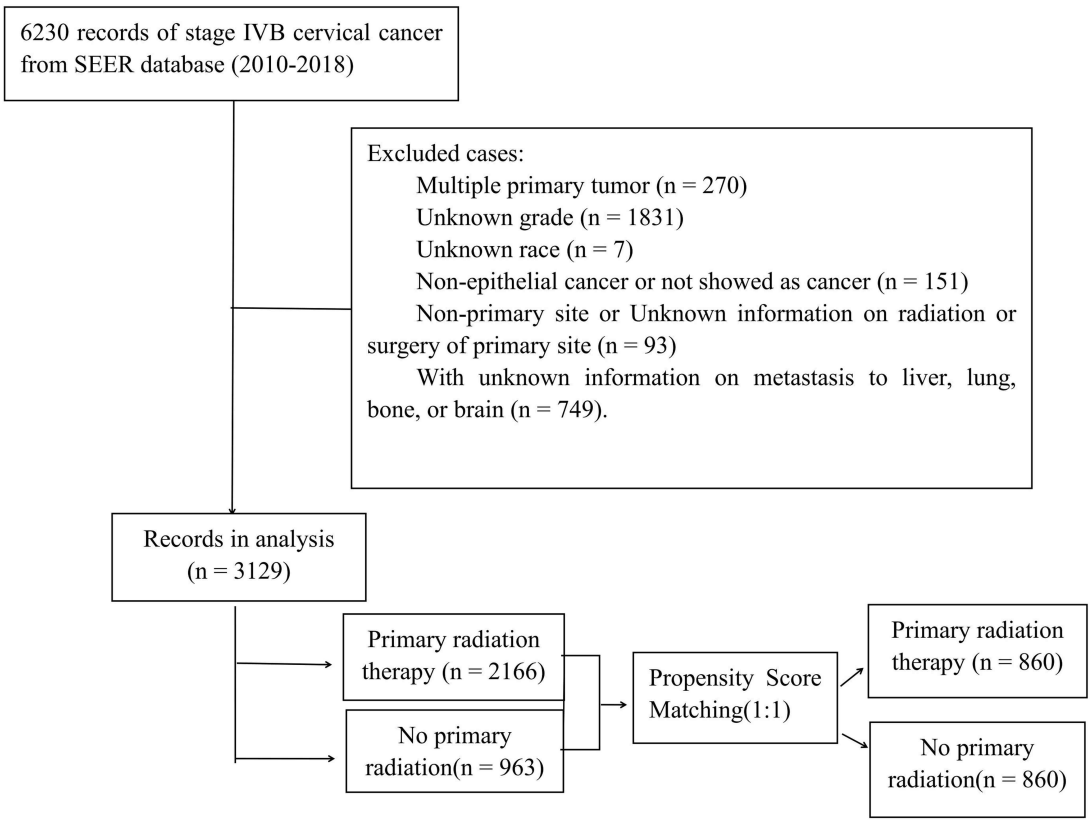

FIGURE 1. Flowchart of data selection. SEER: Surveillance, Epidemiology and End Results.

In this study, the data of patients with stage IVB cervical cancer diagnosed from 2000 to 2018 were retrieved from the SEER database to explore the effects of radiotherapy on their survival and related prognostic factors.

2. Data and methods

2.1 Sources of data

All data in this study were obtained from the SEER database using the SEER* stat software version 8.4.0 (National Cancer Institute, USA). The database includes eighteen cancer registries, representing about twenty-eight percent of the US population. In this study, 6230 cases diagnosed with stage IVB cervical cancer from 2000 to 2018 were selected, and their clinical and pathological data, including age, race, place of residence, histological grading, histological type, site of tumor metastasis, treatment, survival time and current survival status, were assessed. The patient inclusion criteria were (1) diagnosed with squamous cell cancer (SEER Code: 8050-8089) or glandular cancer (SEER Code: 8140-8389); (2) had complete clinical and pathological data; (3) received radiotherapy at the primary site and either surgery or/and chemotherapy; (4) had complete survival information. The exclusion criteria were: (1) presence of multiple primary tumors (n = 270); (2) unknown tumor grade (n = 1831); (3) unknown race (n = 7); (4) non-epithelial cancer or not showed as cancer (n = 151); (5) non-primary site or unknown information on radiation or surgery of primary site (n = 93), (6) with unknown information on metastasis to liver, lung, bone, or brain (n = 749). After the exclusion, 3129 patients with stage IVB cervical cancer were found eligible for this study. Fig. 1 shows a flowchart of case selection.

2.2 statistical analysis

The R software, (version 4.0.2, The R Foundation for Statistical Computing, Vienna, Austria), was used for statistical analysis. The score matching was set at a ratio of 1:1 based on the closest proximity matching method [13, 14]. The standard deviation caliper distance between the nearest neighbor distance and the tendency score logarithm was 0.005. The Kaplan-Meier method was used to plot the surviving curves, which were then compared using the log-rank test. Univariate and multivariate analyses before and after PSM with the Cox ratio risk model were performed to explore independent prognosis factors and map the forest plot. *p*-values less than 0.05 were considered statistically significant.

3. Results

3.1 Clinical as well as pathological features of registered patients

In all, the data of 3129 patients with stage IVB cervical cancer were assessed, of whom 2166 (62.2%) received and 963 did not receive primary radiotherapy. PSM was used to balance their baseline features and avoid selective offset, based on which 860 patients were paired match in a 1:1 ratio and classified into a radiotherapy group and non-radiotherapy group (control group) for survival analysis (Table 1).

TABLE 1. Clinical and pathological characteristics between stage IVB cervical cancer patients with primary radiation therapy and no primary radiation.

	Before PSM			After PSM		
Variables	Primary radiation Therapy (n = 2166) (%)	No primary radiation (n = 963) (%)	*p*	Primary radiation Therapy (n = 860) (%)	No primary radiation (n = 860) (%)	*p*
Age at diagnosis (years)						
<60	1475 (68.1)	558 (57.9)	<0.001	494 (57.4)	512 (59.5)	0.405
≥60	691 (31.9)	405 (42.1)		366 (42.6)	348 (40.5)	
Race						
Black	352 (16.3)	140 (14.5)		125 (14.5)	127 (14.8)	
White	1612 (74.4)	727 (75.5)	0.441	652 (75.8)	647 (75.2)	0.957
Other	202 (9.3)	96 (10.0)		83 (9.7)	86 (10.0)	
Grade						
G1/G2	828 (38.2)	279 (29.0)	<0.001	273 (31.7)	270 (31.4)	0.917
G3/G4	1338 (61.8)	684 (71.0)		587 (68.3)	590 (68.6)	
Histological type						
SCC	1793 (82.8)	708 (73.5)	<0.001	665 (77.3)	650 (75.6)	0.426
Adenocarcinoma	373 (17.2)	255 (26.5)		195 (22.7)	210 (24.4)	
Surgery	485 (22.4)	219 (22.7)	0.865	191 (22.2)	196 (22.8)	0.817
Chemotherapy	1765 (81.5)	482 (50.1)	<0.001	483 (56.2)	482 (56.0)	1.000
Distant organ/site metastasis						
Bone	666 (30.7)	279 (29.0)	0.339	254 (29.5)	255 (29.7)	1.000
Brain	180 (8.3)	75 (7.8)	0.673	61 (7.1)	69 (8.0)	0.523
Liver	321 (14.8)	190 (19.7)	0.001	162 (18.8)	152 (17.7)	0.574
Lung	586 (27.1)	350 (36.3)	<0.001	324 (37.7)	307 (35.7)	0.423
Distant-LN	220 (10.2)	93 (9.7)	0.715	87 (10.1)	89 (10.3)	0.937
Place of residence						
rural	391 (18.1)	170 (17.7)	<0.001	152 (15.8)	162 (18.8)	0.923
urban	1775 (81.9)	793 (82.3)		811 (84.2)	698 (81.2)	

PSM: propensity score matching; LN: lymph node.

3.2 Survival analysis

The K-M curves show that the 5-year survival rate of patients in the non-radiation therapy and radiotherapy group was 4.0% and 10.8% before PSM (HR = 0.54; 95% CI: 0.50–0.59; $p < 0.001$). After PSM, the 5-year survival rate was 4.0% in the non-radiotherapy group and 9.2% in the radiotherapy group (HR = 0.71; 95% CI: 0.64–0.79), and the difference was still statistically significant. Thus, compared with the control group, the survival rate of patients from the radiotherapy group was significantly greater than the non-radiation therapy before and after PSM (Fig. 2).

3.3 Univariate and multivariate Cox analysis

After PSM, univariate Cox analysis showed that age ($p < 0.001$), race ($p < 0.001$), place of residence ($p < 0.001$), histological grade ($p < 0.001$), primary site surgery ($p < 0.001$), systemic chemotherapy ($p < 0.001$), bone metastasis ($p < 0.001$), lung metastasis ($p < 0.001$), liver metastasis ($p < 0.001$) and radiotherapy ($p < 0.001$) were associated with OS. Multivariate analysis showed that race ($p < 0.001$), place of residence ($p < 0.001$), histological grade ($p < 0.001$), primary surgery ($p < 0.001$), systemic chemotherapy($p < 0.001$), bone metastasis ($p < 0.001$), lung metastasis ($p < 0.001$), liver metastasis ($p < 0.001$), and radiotherapy ($p < 0.001$) were independent factors affecting the OS of patients with stage IVB cervical cancer ($p < 0.05$), indicating that age, histological type, brain metastasis, and distant lymph node metastasis had no effect on the OS of the patients after analysis, all these data are shown in Table 2. Cox regression analysis for the 860 matched patients via the forest plots indicated that: (1) The survival effect was presented as HR in this study. The HR value for radiotherapy, chemotherapy and primary surgery was 0.63 (95% CI: 0.56–0.70), 0.43 (95% CI: 0.39–0.48), and 0.42 (95% CI: 0.36–0.48), respectively. (2) Patients with grade G3/G4 and metastasis in bone, liver and lung had significantly increased mortality risk. (3) Survival rates varied by race, with

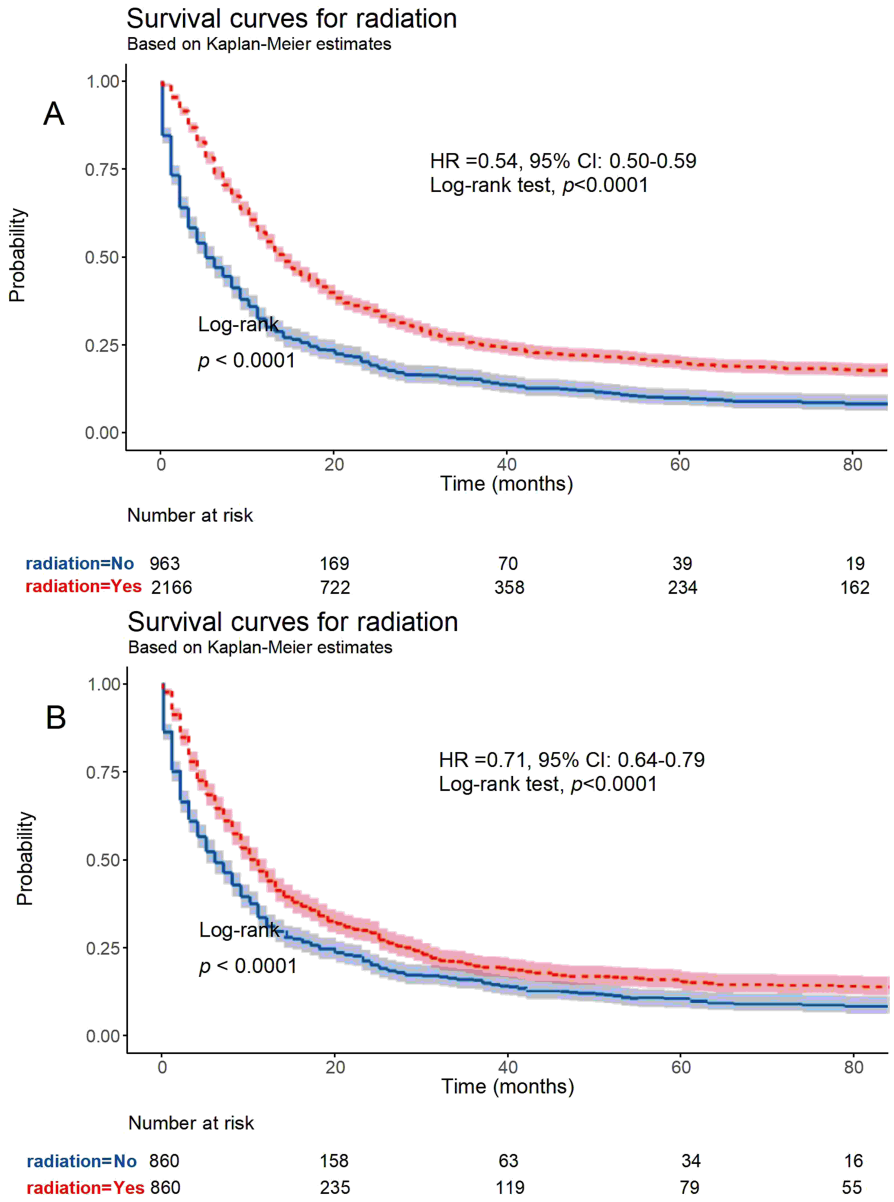

FIGURE 2. Kaplan-Meier survival curves for stage IVB cervical cancer patients with and without radiation therapy. (A) The survival curves of the 3129 patient cohort before propensity score matching (2166 with primary radiation therapy and 963 without primary radiation). (B) The survival curves of 860 cases in the primary radiation therapy group matched in a 1:1 ratio with those from the non-radiation group. HR: hazard ratio; CI: confidence interval.

whites (HR = 0.74, 95% CI: 0.64–0.86) and other races (HR = 0.62, 95% CI: 0.50–0.77) having significantly higher survival rates than blacks ($p < 0.05$). (4) Compared with rural patients, urban patients had higher OS. All these data are shown in Fig. 3.

4. Discussion

Stage IVB cervical cancer is difficult to cure due to the high risk of hematologic metastasis or distant lymph node metastasis. Currently, the most commonly accepted treatment is chemotherapy, which can be combined with other treatments, although multi-drug systemic treatment has shown great improvement in the OS of metastatic cervical cancer [15], tumor progression has been among the most important factor leading to the death of the patients. Based on such observations, we investigated the effects of local radiotherapy on stage IVB cervical cancer and its corresponding influencing factors. The study subjects were stage IVB cervical cancer patients diagnosed from 2000 to 2018 from the SEER database. Our results showed that radiation therapy on the primary tumor could extend their survival time [6, 16, 17] and improve their living quality and local control rate of pelvic metastases. In general, the local invasion of cervical cancer is often accompanied by pain, bleeding, secretions and other symptoms, while improvements in the patients' living quality are often accompanied by improvements in their physical condition, providing more options for treating the metastatic lesions and further improve their prognosis [18]. Other studies showed that the recurrence rates after chemoradiotherapy and chemotherapy were not significantly different [19]. Although concurrent chemoradiotherapy was shown to provide the patients with

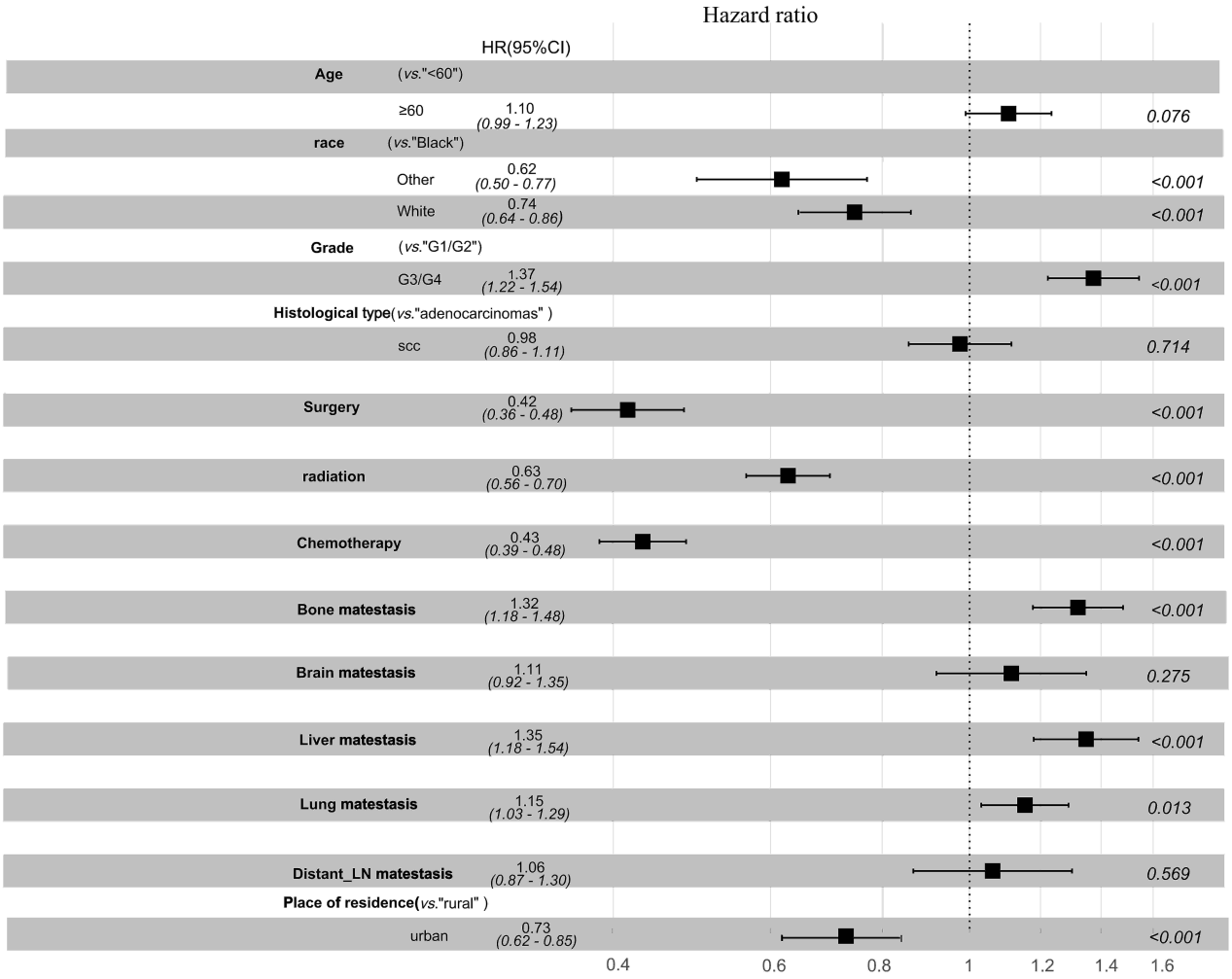

FIGURE 3. Forest plot of factors influencing the survival of the 860 paired patients with cervical cancer. LN: lymph node; HR: hazard ratio; CI: confidence interval.

a longer 5-year progression-free survival(PFS) and OS, their risk of adverse events from radiotherapy also increased [20]. This study demonstrated that primary radiotherapy was an important local treatment with substantial OS benefits, yet it is worth emphasizing that it might not be appropriate for all patients with metastatic cervical cancer [21, 22]. Primary radiotherapy could be more suited for patients with good physical conditions, symptoms of the primary tumor, and a low systemic tumor burden.

In this study, the proportion of patients with a survival time of more than 5 years after primary radiotherapy was about 10%, and chemotherapy was identified as an independent prognostic factor in these patients. However, the proportion of patients with 5 years of OS who received radiotherapy with or without chemotherapy was lower than that in the study of Venigalla *et al.* [21], who reported that although the treatment techniques and the systemic treatment were improved, the overall prognosis of metastatic cervical cancer was still poor (5-year OS rate ~15%). In this present study, our results showed that race, histological grade, primary surgical site, radiotherapy at the primary tumor, systemic chemotherapy, bone metastasis, lung metastasis, and liver metastasis were independent factors affecting the OS of stage IVB cervical cancer. We also observed that the primary tumor surgery was positively correlated with the OS of stage IVB cervical cancer patients. Further, local therapy (primary surgery or radiotherapy) improved OS because it could increase local control and decrease the risk of life-threatening events such as tumor progression, bleeding or invasion to adjacent structures like the rectum and bladder [23]. Moreover, the local therapy could reduce the risk of tumor progression by controlling the core lesion, which could further prevent tumor metastasis at new sites [21, 24]. Lastly, animal models indicated that reducing the cells in the core lesion *via* radical topical therapy might reverse tumor-associated immunosuppression [25]. There is now increasing evidence showing that the local treatment (radiotherapy or surgery) of the primary lesion could prolong the survival of metastatic cervical cancer [26–31] and decrease the mortality rate by nearly 30%, the median survival was 3 to 4 months longer [26, 27, 32]. However, surgery might not be suitable for all patients. Similar to primary tumor radiotherapy, primary tumor surgery might be more suitable for patients with good physical conditions, small metastatic tumor burden and obvious primary tumor symptoms.

TABLE 2. Cox proportional hazards regression analysis of patients with stage IVB cervical cancer before and after propensity score matching.

Variables	Before PSM				After PSM			
	Univariate Cox analysis		Multivariate Cox analysis		Univariate Cox analysis		Multivariate Cox analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years) ("<60" as reference)								
≥60	1.42 (1.30–1.54)	<0.001	1.14 (1.04–1.24)	0.003	1.31 (1.18–1.46)	<0.001	1.10 (0.99–1.23)	0.076
Race ("Black" as reference)								
White	0.75 (0.67–0.83)	<0.001	0.78 (0.70–0.87)	<0.001	0.66 (0.57–0.76)	<0.001	0.74 (0.64–0.86)	<0.001
Other	0.76 (0.64–0.89)	0.001	0.70 (0.59–0.83)	<0.001	0.61 (0.49–0.76)	<0.001	0.62 (0.50–0.77)	<0.001
Grade ("Grade1/2" as reference)								
G3/G4	1.31 (1.21–1.43)	<0.001	1.30 (1.19–1.41)	<0.001	1.27 (1.14–1.43)	<0.001	1.37 (1.22–1.54)	<0.001
Surgery ("No" as reference)	0.46 (0.41–0.51)	<0.001	0.45 (0.40–0.50)	<0.001	0.40 (0.35–0.46)	<0.001	0.42 (0.36–0.48)	<0.001
Radiation ("No" as reference)	0.54 (0.50–0.59)	<0.001	0.64 (0.58–0.70)	<0.001	0.71 (0.64–0.79)	<0.001	0.63 (0.56–0.70)	<0.001
Chemotherapy ("No" as reference)	0.38 (0.35–0.42)	<0.001	0.43 (0.39–0.47)	<0.001	0.45 (0.41–0.50)	<0.001	0.43 (0.39–0.48)	<0.001
Metastasis to ("No" as reference)								
Bone	1.14 (1.05–1.24)	0.002	1.26 (1.15–1.37)	<0.001	1.30 (1.16–1.46)	<0.001	1.32 (1.18–1.48)	<0.001
Brain	1.13 (0.99–1.30)	0.075	1.18 (1.03–1.36)	0.017	1.19 (0.98–1.44)	0.075	1.11 (0.92–1.35)	0.275
Liver	1.42 (1.28–1.58)	<0.001	1.36 (1.22–1.51)	<0.001	1.33 (1.17–1.52)	<0.001	1.35 (1.18–1.54)	<0.001
Lung	1.45 (1.33–1.58)	<0.001	1.26 (1.15–1.38)	<0.001	1.21 (1.08–1.35)	0.001	1.15 (1.03–1.29)	0.013
Distant-LN	0.97 (0.84–1.13)	0.732	1.22 (1.05–1.43)	0.011	0.84 (0.69–1.02)	0.074	1.06 (0.87–1.30)	0.569
Histological type ("Adenocarcinoma" as reference)								
SCC	1.09 (0.99–1.21)	0.085	1.00 (0.90–1.11)	1.000	1.29 (1.14–1.47)	<0.001	0.98 (0.86–1.11)	0.714
Place of residence ("rural" as reference)								
urban	0.74 (0.66–0.82)	<0.001	0.76 (0.68–0.84)	<0.001	0.68 (0.58–0.78)	<0.001	0.73 (0.62–0.85)	<0.001

PSM: propensity score matching; HR: hazard ratio; CI: confidence interval; SCC: squamous cell carcinoma antigen; LN: lymph node.

Presently, chemotherapy is recognized as the main treatment for stage IVB cervical cancer. Our findings indicated that chemotherapy could extend the survival of metastatic cervical cancer patients. Several studies showed that patients who responded to chemotherapy had a longer survival time than non-respondents. Therefore, appropriate chemical therapy could prolong the survival and prognosis of metastatic cervical cancer patients [28, 33]. However, chemotherapy alone might still be inadequate due to limited efficacy and poor response [34, 35].

Nishio *et al.* [36] stated that racial differences in cervical cancer incidence and death rates were indisputable, consistent with our findings showing that racial differences affected patients' OS. However, the reasons for racial differences in mortality rates remain unclear and controversial. Some researchers hypothesized that biological differences among different races might be responsible for the different susceptibility to diseases [37], while others believe that social economy and culture might have certain impacts on the occurrence of the disease [38]. In this study, we found that black people had a worse stage IVB cervical cancer survival rate than whites and other ethnic groups in the United States. We believe this might be because black Americans did not have similar access to the same prevention, diagnosis, treatment, *etc.*, as people of other races. It could also be because blacks have a worse biological prognosis of cervical cancer [39, 40]. Further, we also found that rural residents had a higher mortality rate than urban residents. Compared with urban areas, rural public health facilities were poor, rural women had relatively lesser awareness of self-health care, and it was relatively difficult to seek medical treatment, *etc.*, thereby leading to untimely medical treatment and subsequent higher mortality rates [41]. Public health status was inversely associated with cervical cancer mortality [42, 43], Public health conditions include health facilities, health promotion, screening, prevention, diagnosis and treatment conditions, cervical cancer incidence and mortality were lower in regions with better public health status. Relatively poor public health status was an important factor for the high mortality rate of rural residents. Cohen *et al.* [44] made similar observations and reported that cervical cancer incidence and death rates varied widely based on geographical differences. They also suggested a link between geography and ethnicity as different geographical locations had different social, economic, cultural and racial differences. This might be one of the reasons for the observation of worse survival time of black Americans compared with white Americans and other races and the higher mortality rate of rural residents compared with urban residents observed in our study. Thus, we hope these results could guide related authorities to further strategize the prevention and treatment of cervical cancer.

Previous studies indicated that age, histological type and site of distant organ metastasis were important prognostic factors affecting the survival of stage IVB cervical cancer patients [45, 46]. Some studies also found that younger patients had better OS than older patients [22, 27]. However, Nishio *et al.* [36] found no effect of age on stage IVB cervical cancer survival, which was consistent with our study, indicating that this should be further clarified in future studies. In cervical cancer, squamous cell carcinoma and adenocarcinoma are the most common subtype of cervical cancer, accounting for 70% and 25% of all cervical cancer, respectively [47]. Other histological types are not discussed because they account for only a small proportion of cervical cancer. In some reports, cervical adenocarcinoma had a worse prognosis than squamous cell carcinoma [48, 49]. However, our study found no significant difference between the survival of squamous cell carcinoma and adenocarcinoma patients. which was consistent with the study of Emmett *et al.* [50]. The effect of histological types on survival of stage IVB cervical cancer is still controversial, and more data are needed to study this issue in the future. Our findings also showed that bone metastasis, lung metastasis and liver metastasis were independent factors affecting the survival of stage IVB cervical cancer patients. Previous studies indicated that the 5-year OS of cervical cancer patients with lung metastasis ranged between 0 to 60 months. Hwang *et al.* [53] reported that the median survival time after diagnosis of brain metastasis was only 5.9 months [51, 52], and that after bone metastases was about 5.5 to 12 months. Comparatively, our results showed that brain metastasis was not an independent factor affecting the survival of stage IVB cervical cancer, which may be related to the much shorter survival time after diagnosis with brain, lung, liver and bone metastases. However, due to limited reports, larger cohort studies are required to further clarify the impact of different metastatic locations of cervical cancer on the patients' survival.

There were some limitations in this study that should be clarified. First, our results might have been impacted by the retrospective nature and long duration of the retrieved data. Second, it is well-known that the prognosis of stage IVB cervical cancer is related to primary tumor size, patients' physical condition, burden of distant metastasis, and other surgical-related factors. Since the SEER database does not have these parameters, we could not perform deeper analyses to investigate their influence in this study cohort. Third, there were no detailed data on radiation therapy, including dosage, duration, technique and combination mode with chemotherapy, in the SEER database, which should be explored in future studies to determine their significance on the patients.

5. Conclusions

This study shows that primary radiotherapy could prolong the OS of stage IVB cervical cancer and that primary radiotherapy was beneficial to the patients. However, these conclusions should be clarified in larger cohorts of patients using better-designed studies such as in prospective and randomized settings.

AUTHOR CONTRIBUTIONS

DMW—contributed to conceptualization, methodology, data analyses, writing original draft, writing review and editing, supervision, and project administration. BX—contributed to methodology, data analyses, validation, writing review and editing, and project administration. DHL—contributed to investigation, resources, data analyses, editing, supervision, and project administration. YZ and XQC—contributed to software, validation, data analyses, data curation, writing orig-

inal draft, and project administration. GPS—contributed to conceptualization, methodology, validation, resources, writing review and editing, visualization, supervision, and project administration.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Drolet M, Bénard É, Pérez N, Brisson M. Population level-impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Obstetrical & Gynecological Survey. 2019; 74: 590–592.

[2] Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. European Journal of Cancer. 2013; 49: 3262–3273.

[3] Siegel RL, Miller KD, Jemal A. Cancer statisties. CA: A Cancer Journal for Clinicians. 2016; 66: 7–30.

[4] Siegel RL, Naishadham D, Jemal A. Cancer statisties. CA: A Cancer Journal for Clinicians. 2013; 63: 11–30.

[5] Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. Journal of Gynecologic Oncology. 2016; 27: e43.

[6] Yin Z, Lou H, Tang H, Ni J, Zhou Q, Chen M. Efficacy of radical doses of pelvic radiotherapy for primary tumor treatment in patients with newly diagnosed organ metastatic cervical cancer. Radiation Oncology. 2019; 14: 82.

[7] Meir H, Kenter G, Burggraaf J, Kroep J, Welters M, Melief C, *et al*. The need for improvement of the treatment of advanced and metastatic cervical cancer, the rationale for combined chemo-immunotherapy. Anti-Cancer Agents in Medicinal Chemistry. 2014; 14: 190–203.

[8] Friedlander M, Grogan M. Guidelines for the treatment of recurrent and metastatic cervical cancer. The Oncologist. 2002; 7: 342–347.

[9] Chao A, Lin C, Lai C. Updates in systemic treatment for metastatic cervical cancer. Current Treatment Options in Oncology. 2014; 15: 1–13.

[10] Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, *et al*. The European society of gynaecological oncology/european society for radiotherapy and oncology/european society of pathology guidelines for the management of patients with cervical cancer. Radiotherapy and Oncology. 2018; 127: 404–416.

[11] Serkies K, Jassem J. Systemic therapy for cervical carcinoma—current status. Chinese Journal of Cancer Research. 2018; 30: 209–221.

[12] Zanini LAG, Reis RJ, Laporte GA, Vieira SC, Zanella JF, Machado GM. Analysis of the surgical management of patients with recurrent cervical cancer after radiotherapy and chemotherapy. Journal of Brazilian College of Surgeons. 2020; 47: e20202443.

[13] Chien S, Liu C, Hu Y, Hong Y, Teng C, Yeh C, *et al*. Frequency of surveillance computed tomography in non-Hodgkin lymphoma and the risk of secondary primary malignancies: a nationwide population-based study. International Journal of Cancer. 2015; 137: 658–665.

[14] Nassour I, Wang SC, Christie A, Augustine MM, Porembka MR, Yopp AC, *et al*. Minimally invasive versus open pancreaticoduodenectomy. Annals of Surgery. 2018; 268: 151–157.

[15] Scatchard K, Forrest JL, Flubacher M, Cornes P, Williams C. Chemotherapy for metastatic and recurrent cervical cancer. The Cochrane Database of Systematic Reviews. 2012; 10: CD006469.

[16] Ning MS, Ahobila V, Jhingran A, Stecklein SR, Frumovitz M, Schmeler KM, *et al*. Outcomes and patterns of relapse after definitive radiation therapy for oligometastatic cervical cancer. Gynecologic Oncology. 2018; 148: 132–138.

[17] Rusthoven CG, Jones BL, Flaig TW, Crawford ED, Koshy M, Sher DJ, *et al*. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. Journal of Clinical Oncology. 2016; 34: 2835–2842.

[18] Reck M, Thatcher N, Smit EF, Lorigan P, Szutowicz-Zielinska E, Liepa AM, *et al*. Baseline quality of life and performance status as prognostic factors in patients with extensive-stage disease small cell lung cancer treated with pemetrexed plus carboplatin *vs.* etoposide plus carboplatin. Lung Cancer. 2012; 78: 276–281.

[19] Kim HS, Kim T, Lee ES, Kim HJ, Chung HH, Kim JW, *et al*. Impact of chemoradiation on prognosis in stage IVB cervical cancer with distant lymphatic metastasis. Cancer Research and Treatment. 2013; 45: 193–201.

[20] Jeon W, Koh HK, Kim HJ, Wu H, Kim JH, Chung HH. Salvage radiotherapy for lymph node recurrence after radical surgery in cervical cancer. Journal of Gynecologic Oncology. 2012; 23: 168.

[21] Venigalla S, Guttmann DM, Horne ZD, Carmona R, Shabason JE, Beriwal S. Definitive local therapy is associated with improved overall survival in metastatic cervical cancer. Practical Radiation Oncology. 2018; 8: e377–e385.

[22] Ding L, Bi Z, Pan Z, Yu X, Zhao X, Bai S, *et al*. Brachytherapy-based radiotherapy is associated with improved survival for newly diagnosed metastatic cervical cancer. Brachytherapy. 2021; 20: 361–367.

[23] Perkins V, Moore K, Vesely S, Matsuo K, Mostofizadeh S, Sims TT, *et al*. Incorporation of whole pelvic radiation into treatment of stage IVB cervical cancer: a novel treatment strategy. Gynecologic Oncology. 2020; 156: 100–106.

[24] Comen E, Norton L, Massagué J. Clinical implications of cancer self-seeding. Nature Reviews Clinical Oncology. 2011; 8: 369–377.

[25] Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Research. 2004; 64: 2205–2211.

[26] Wang Y, Farmer M, Izaguirre EW, Schwartz DL, Somer B, Tillmanns T, *et al*. Association of definitive pelvic radiation therapy with survival among patients with newly diagnosed metastatic cervical cancer. JAMA Oncology. 2018; 4: 1288.

[27] Huang K, Jia M, Li P, Han J, Zhang R, Li Q, *et al*. Radiotherapy improves the survival of patients with metastatic cervical cancer: a propensity-matched analysis of SEER database. International Journal of Gynecologic Cancer. 2018; 28: 1360–1368.

[28] Hata M, Koike I, Miyagi E, Asai-Sato M, Kaizu H, Mukai Y, *et al*. Radiation therapy for patients with bone metastasis from uterine cervical cancer: its role and optimal radiation regimen for palliative care. Anticancer Research. 2018; 38: 1033–1040.

[29] Shi X, Huang N- S, Shi R- L, Wei WJ, Wang YL, Ji QH. Prognostic value of primary tumor surgery in minor salivary- gland carcinoma patients with distant metastases at diagnosis: first evidence from a SEER-based study. Cancer Management and Research. 2018; 10: 2163–2172.

[30] Luo D, Liu Q, Yu W, Ma Y, Zhu J, Lian P, *et al*. Prognostic value of distant metastasis sites and surgery in stage IV colorectal cancer: a population-based study. International Journal of Colorectal Disease. 2018; 33: 1241–1249.

[31] Chen J, Kong Y, Weng S, Dong C, Zhu L, Yang Z, *et al*. Outcomes of surgery for gastric cancer with distant metastases: a retrospective study from the SEER database. Oncotarget. 2017; 8: 4342–4351.

[32] Wang Y, Ouyang Y, Su J, Bai Z, Cai Q, Cao X. Role of locoregional surgery in treating FIGO 2009 stage IVB cervical cancer patients: a population-based study. BMJ Open. 2021; 11: e042364.

[33] Saijo N. Chemotherapy against pulmonary metastasis from uterine cervical carcinoma. Gan To Kagaku Ryoho,Cancer & chemotherapy. 1982; 9: 992–997.
[34] Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, *et al*. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a gynecologic oncology group study. Journal of Clinical Oncology. 2009; 27: 4649–4655.
[35] Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, *et al*. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. Journal of Clinical Oncology. 2015; 33: 2129–2135.
[36] Nishio S, Matsuo K, Yonemoto K, Shimokawa M, Hosaka M, Kodama M, *et al*. Race and nodal disease status are prognostic factors in patients with stage IVB cervical cancer. Oncotarget. 2018; 9: 32321–32330.
[37] Goldson A, Henschke U, Leffall LD, Schneider RL. Is there a genetic basis for the differences in cancer incidence between Afro-Americans and Euro-Americans? Journal of the National Medical Association.1981; 73: 701–706.
[38] Clegg LX, Reichman ME, Miller BA, Hankey BF, Singh GK, Lin YD, *et al*. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: national longitudinal mortality study. Cancer Causes & Control. 2009; 20: 417–435.
[39] Somayaji D, Cloyes KG. Cancer fear and fatalism. Cancer Nursing. 2015; 38: 133–144.
[40] Collins Y, Holcomb K, Chapman-Davis E, Khabele D, Farley JH. Gynecologic cancer disparities: a report from the health disparities taskforce of the society of gynecologic oncology. Gynecologic Oncology. 2014; 133: 353–361.
[41] Jing H, Xianghong Y, Ai L, Wenjuan Z. Problems and countermeasures in the implementation of national cervical and breast screening program for women in rural areas. Chinese General Practice. 2020; 23: 1680–1686.
[42] Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, *et al*. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. The Lancet Infectious Diseases. 2017; 17: 1293–1302.
[43] Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, *et al*. ICO/IARC information centre on HPV and cancer (HPV information centre). Human Papillomavirus and Related Diseases in China. 2019; 17: 23-25.
[44] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. The Lancet. 2019; 393: 169–182.
[45] Sasano T, Mabuchi S, Kuroda H, Takahashi R, Kozasa K, Isohashi F, *et al*. Predictors of survival in patients with FIGO stage IVB cervical cancer. International Journal of Gynecological Cancer. 2016; 26: 528–533.
[46] Usami T, Takahashi A, Matoda M, Okamoto S, Kondo E, Kanao H, *et al*. Review of treatment and prognosis of stage IVB cervical carcinoma. International Journal of Gynecologic Cancer. 2016; 26: 1239–1245.
[47] Small W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, *et al*. Cervical cancer: a global health crisis. Cancer. 2017; 123: 2404–2412.
[48] Lim MC, Lee H, Seo S, Kim MS, Kim J, Zo JI, *et al*. Pathologic diagnosis and resection of suspicious thoracic metastases in patients with cervical cancer through thoracotomy or video-assisted thoracic surgery. Gynecologic Oncology. 2010; 116: 478–482.
[49] Seki M, Nakagawa K, Tsuchiya S, Matsubara T, Kinoshita I, Weng S, *et al*. Surgical treatment of pulmonary metastases from uterine cervical cancer. The Journal of Thoracic and Cardiovascular Surgery. 1992; 104: 876–881.
[50] Emmett M, Gildea C, Nordin A, Hirschowitz L, Poole J. Cervical cancer—does the morphological subtype affect survival rates? Journal of Obstetrics and Gynaecology. 2018; 38: 548–555.
[51] González Casaurrán G, Simón Adiego C, Peñalver Pascual R, Moreno Mata N, Lozano Barriuso MÁ, González Aragoneses F. Surgery of female genital tract tumour lung metastases. Archivos de Bronconeumología. 2011; 47: 134–137.
[52] Hwang JH, Yoo HJ, Lim MC, Seo S, Kang S, Kim J, *et al*. Brain metastasis in patients with uterine cervical cancer. Journal of Obstetrics and Gynaecology Research. 2013; 39: 287–291.
[53] Matsumiya H, Todo Y, Okamoto K, Takeshita S, Yamazaki H, Yamashiro K, *et al*. A prediction model of survival for patients with bone metastasis from uterine cervical cancer. Journal of Gynecologic Oncology. 2016; 27: e55.

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