

Original Article



Surgery of primary sites for stage IVB cervical cancer patients receiving chemoradiotherapy: a population-based study

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Conflict of Interest

No potential conflict of interest relevant to this
article was reported.

ABSTRACT

Objective: The purpose of this study was to analyze the impact of surgery of primary sites on stage IVB cervical cancer patients from a population-based database, the Surveillance, Epidemiology and End Results (SEER).

Methods: Propensity score matching was performed to minimize heterogeneity in patient between with-surgery group and without-surgery group. Clinicopathological characteristics were compared using the χ^2 or Fisher's exact test. Survival analysis included the Kaplan-Meier method, log-rank test, and Cox proportional hazards model.

Results: Between 2010-2015, a total of 1,139 International Federation of Gynecology and Obstetrics (FIGO) stage IVB cervical cancer patients receiving chemoradiotherapy (CRT) were included in this retrospective study. Within post-matching cohort, the median duration of overall survival (OS) in stage IVB cervical cancer patients receiving CRT was 22 months. The overall 5-year survival rate was 25.7%. The increasing American Joint Committee on Cancer T stage (T1 vs. T2, $p=0.033$, hazard ratio [HR]=1.79, 95% confidence interval [CI]=1.05–3.05; T1 vs. T3, $p=0.003$, HR=2.20, 95% CI=1.31–3.67; T1 vs. T4, $p=0.037$, HR=2.75, 95% CI=1.06–7.12) and visceral metastasis (with vs. without, $p=0.038$, HR=1.60, 95% CI=1.03–2.49) was reported as independent risk factors of OS. Surgery of primary sites combined with CRT tended to prolong the survival of stage IVB cervical cancer patients ($p<0.001$, HR=0.36, 95% CI=0.21–0.61) compared with CRT, especially for patients without visceral metastasis ($p=0.005$, HR=0.31, 95% CI=0.14–0.70).

Conclusions: In conclusion, patients with stage IVB cervical cancer may achieve their best outcomes through CRT combined with surgery of primary sites. However, it deserves large scale prospective clinical trials to confirm.

Keywords: Cervical Cancer; Metastatic; Chemoradiotherapy; Surgery

INTRODUCTION

In China, it is estimated that approximately 98.9/1,000 new cases will be diagnosed with cervical cancer in 2015, while approximately 30.5/1,000 women would die from this disease. It ranks as the second most commonly diagnosed cancer among Chinese women

Author Contributions

Conceptualization: L.H., C.X.; Data curation: P.Y.; Formal analysis: L.H.; Investigation: L.H., P.Y.; Methodology: L.H., C.X.; Project administration: L.H., P.Y.; Supervision: C.X.; Validation: P.Y.; Writing - original draft: L.H.; Writing - review & editing: C.X.

[1]. According to the International Federation of Gynecology and Obstetrics (FIGO version 2009), stage IVB cervical cancer patients (disseminated cervical cancer) are classified as diagnosed with distant metastasis as the first manifestation [2]. Patients who develop distant metastases are rarely curable. The 5-year survival of stage IVB patients is poor and approximately 50% of these patients show a fatal outcome within 1 year [3-5].

No standard treatment is available for patients with stage IVB cervical cancer compared with locally advanced cervical cancer. International guidelines propose cisplatin-based combination chemotherapy for widespread metastatic disease with possible addition of bevacizumab. Chemotherapy is useful for the treatment of recurrent or stage IVB cervical cancer who are not candidates for radiation or extensive surgery [6]. However, either bevacizumab or traditional chemotherapy have shown unsatisfactory effect on eliminating the primary cervical cancer and metastases. Even worse, responses to chemotherapy are often of short duration. In patients with stage IVB cervical cancer, the combined use of radiotherapy and chemotherapy has already been proved to improve survival than previously reported [7-9]. However, the role of surgery in treating stage IVB patients is still in controversy and has not been fully illustrated. Therefore, in the present study, we tried to analyze the impact of surgery of primary sites on stage IVB cervical cancer patients from a population-based database, the Surveillance, Epidemiology and End Results (SEER). We compared the outcomes of stage IVB cervical cancer patients receiving chemoradiotherapy (CRT) alone and surgery combined with CRT, which may contribute to clinical practice.

MATERIALS AND METHODS

1. Data source

The SEER database, a population-based registry, is sponsored by the National Cancer Institute. With 18 population-based cancer registries, the SEER program covers approximately 28% of the cancer registries from the United States [10,11]. The National Cancer Institute's SEER*Stat software (version 8.3.5; Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat) was used to extract data after access permitted by signing an agreement. In view of that SEER database is an open public database, written informed consent cannot be assessed.

2. Study population

Information of stage IVB cervical cancer patients from 2010–2015 was retrieved from the recent SEER-18 database. We limited this study to patients diagnosed between 2010 and 2015 as detailed information about site-specific metastasis was not recorded before 2010. Since 2010, the SEER data provides the only four specific sites of metastases (bone, brain, liver, and lung). Other sites of metastasis are not documented currently. Only newly diagnosed IVB cervical cancers were included in the study. We included site codes C53.0–C53.1, C53.8, and C53.9 to identify primary cervical cancer based on the International Classification of Diseases for oncology, third Edition (ICD-O-3).

We collected the basic characteristics of these patients included age at diagnosis; year of diagnosis (between 2010–2015); race (white, black or others including Asian or Pacific Islander, American Indian/Alaska Native); marital status (married or unmarried); insurance record (insured or uninsured); tumor grade, I–II (including G1 or well-differentiated, G2 or moderately-differentiated), III–IV (including G3 or poorly-differentiated, G4 or

undifferentiated or anaplastic); tumor histology (squamous cell carcinoma, adenocarcinoma, and others types including epithelial neoplasms, transitional cell papillomas and carcinomas, cystic, mucinous and serous neoplasms, complex epithelial neoplasms, complex mixed and stromal neoplasms and unspecified neoplasms); American Joint Committee on Cancer (AJCC) stage; tumor size (The SEER databased records the most accurate measurement of a solid primary tumor, usually measured on the surgical resection specimen); site-specific metastasis (lung, bone, liver, and brain); cause-specific death classification; vital status; and survival months. Patients with visceral metastasis means patients were diagnosed with any organ metastasis including lung, bone, liver and brain.

In addition, treatment data were retrieved for each case included chemotherapy, radiotherapy, and surgery (including primary sites and metastatic sites). We selected patients who both underwent chemotherapy and radiotherapy. Surgery procedure was classified as surgery of primary sites and surgery of metastatic sites.

Surgery procedure of primary sites including Loop Electrocautery Excision Procedure (LEEP), local tumor excision, total hysterectomy (simple, pan-) without removal of tubes and ovaries, total hysterectomy (simple, pan-) with removal of tubes and/or ovary, radical or extended hysterectomy including modified radical or extended hysterectomy, radical hysterectomy and extended radical hysterectomy, hysterectomy and pelvic exenteration. To explore the role of non-diagnostic surgery in stage IVB cervical cancer patients, we only included patients underwent radical or extended hysterectomy and pelvic exenteration. We finally included only two groups in our analysis, surgery of primary sites with CRT group (with-surgery group) and CRT alone group (without surgery group).

3. Statistical analysis

Data analysis was performed using SPSS ver. 24.0 (SPSS Inc., Chicago, IL, USA) and R (version 3.2.4). Clinico-pathologic characteristics between different groups of patients were compared using the χ^2 or Fisher exact test. Propensity matching was performed in R 3.2.4 using the nearest neighbor matching to lessen the effects of confounding factors including age at diagnosis, race, marital status, insurance record, grade, histology, tumor size, AJCC T stage, AJCC N stage, visceral metastasis. The Kaplan-Meier method was used to obtain estimates of survival. The survival curves were made by GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA). The primary outcome of the survival analysis was the overall survival (OS; survival months), which was defined from the time of diagnosis of uterine cervical cancer to causes of death. The differences in OS were compared using the log-rank test. Cox regression models were used to estimate the main effects of clinical factors for patients' survival. A probability value of less than 0.05 was considered statistically significantly different.

RESULTS

1. Patients' characteristics

A flow-chart of the study design is shown in **Fig. 1**. Between 2010 and 2015, a total of 2,733 patients with stage IVB cervical cancer were identified from the SEER database. Patients with one more primary malignant tumors (n=333), died of other causes (n=119), and survival months were 0 (n=196) were excluded from this study. We also excluded patients whose information was collected from autopsy and death certificates (n=2), with unknown race

(n=3), with no evidence of primary tumor (AJCC, T0, n=7) and with unknown information of surgery (n=3). In terms of treatment modalities, we also excluded patients without radiotherapy or chemotherapy (n=926), with surgery of metastatic sites only (n=5) and a total of 1,139 patients who underwent CRT were included in this study. The detailed information of surgery of primary sites was listed in **Supplementary Fig. 1**. In terms of specific surgery procedure, diagnostic surgery (n=137) should be excluded and finally 1,002 patients were included in this study. The baseline characteristics of 1,002 patients were shown in **Supplementary Table 1**. We divided patients into two groups, with-surgery group

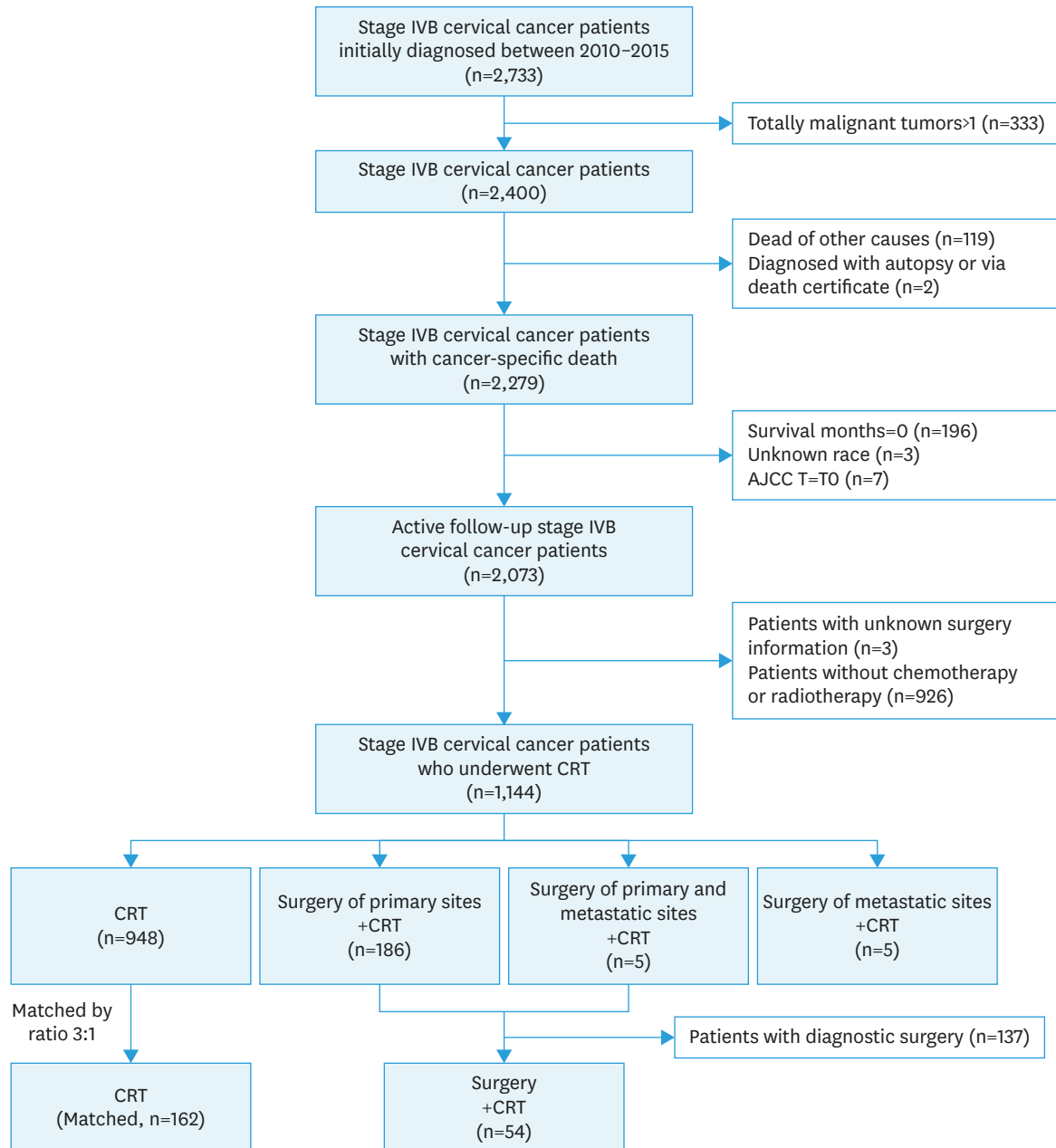


Fig. 1. The flowchart of this study. AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy.

(n=54) and without surgery group (n=948). However, there is significant difference between without-surgery group and with-surgery group concerning baseline demographic and clinicopathologic characteristics. Younger married patients with the White race, grade III–IV, squamous carcinoma, tumor size less than 4 cm and lower aggressive level of AJCC T stage are more likely to receive surgery of primary sites.

To make the patients in each group comparable, we then used the methodology of matching to balance the prognostic factors between two groups. After matching, 162 patients of 948 patients without surgery were left. The detailed information of clinical characteristics of two group of patients were shown in **Table 1**. As a result, there existed no statistical difference between two groups.

Table 1. Baseline demographic and clinicopathological characteristics of stage IVB cervical cancer receiving CRT (matched)

Characteristic	Without Surgery (n=162)	With surgery (n=54)	p-value
Median age at diagnosis	50	49	0.664
Race			0.224
White	123 (75.9)	47 (87.0)	
Black	23 (14.2)	4 (7.4)	
Others*	16 (9.9)	3 (5.6)	
Marital Status			0.748
No	72 (44.4)	22 (40.7)	
Yes	78 (48.1)	29 (53.7)	
Unknown	12 (7.4)	3 (5.6)	
Insurance Record			0.470
No	17 (10.5)	4 (7.4)	
Yes	142 (87.7)	50 (92.6)	
Unknown	3 (1.9)	0 (0.0)	
Grade			0.306
I–II	72 (44.4)	20 (37.0)	
III–IV	68 (42.0)	29 (53.7)	
Unknown	22 (13.6)	5 (9.3)	
Histology			0.612
SCC	95 (58.6)	28 (51.9)	
Adenocarcinoma	37 (22.8)	13 (24.1)	
Other†	30 (18.5)	13 (24.1)	
Tumor size (cm)			0.754
≤4	114 (70.4)	38 (70.4)	
>4	32 (19.8)	9 (16.7)	
Unknown	16 (9.9)	7 (13.0)	
AJCC T stage			0.592
T1	61 (37.7)	17 (31.5)	
T2	47 (29.0)	21 (38.9)	
T3	46 (28.4)	14 (25.9)	
T4	8 (4.9)	2 (3.7)	
AJCC N stage			0.563
N0	43 (26.5)	11 (20.4)	
N1	114 (70.4)	42 (77.8)	
Nx	5 (3.1)	1 (1.9)	
Visceral metastasis			0.887
No	93 (57.4)	29 (53.7)	
Yes	57 (39.5)	23 (42.6)	
Unknown	5 (3.1)	2 (3.7)	
Median OS (mo)	19	32	

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; NOS, not otherwise specified; OS, overall survival; SCC, squamous cell carcinoma.

*Race–others (Asian or Pacific Islander, American Indian/Alaska Native); †Histology–others (epithelial neoplasms, NOS; transitional cell papillomas and carcinomas; cystic, mucinous and serous neoplasms; complex epithelial neoplasms; complex mixed and stromal neoplasms; unspecified neoplasms).

2. Survival analysis

The median OS in stage IVB cervical cancer patients who received CRT was 22 months. The overall 3-year survival rate was 31.3%. The overall 5-year survival rate was 25.7%.

In univariate analysis, significant difference was found in prognostic factors related to OS including race (white vs. black, $p=0.038$, hazard ratio [HR]=1.72, 95% confidence interval [CI]=1.03–2.88), AJCC T stage (T1 vs. T3, $p=0.003$, HR=2.05, 95% CI=1.27–3.31; T1 vs. T4, $p=0.006$, HR=3.53, 95% CI=1.44–8.65), visceral metastasis (with vs. without, $p<0.001$, HR=1.95, 95% CI=1.32–2.86) and treatment (without surgery vs. with surgery, $p=0.002$, HR=0.47, 95% CI=0.29–0.76) (**Table 2**). We then performed multivariate Cox regression analysis, increasing AJCC T stage (T1 vs. T2, $p=0.033$, HR=1.79, 95% CI=1.05–3.05; T1 vs.

Table 2. The association of demographic and clinicopathological characteristics with OS in stage IVB cervical cancer patients receiving CRT (matched)

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis				
≤50	-		-	
>50	0.87 (0.59–1.28)	0.479	0.75 (0.40–1.41)	0.373
Race				
White	-		-	
Black	1.72 (1.03–2.88)	0.038	1.53 (0.82–2.85)	0.177
Other*	1.19 (0.63–2.24)	0.586	1.79 (0.90–3.60)	0.100
Marital Status				
No	-		-	
Yes	0.92 (0.61–1.37)	0.667	0.80 (0.35–1.84)	0.432
Insurance Record				
No	-		-	
Yes	0.70 (0.39–1.29)	0.255	0.61 (0.29–1.25)	0.177
Grade				
I–II	-		-	
III–IV	0.58 (0.30–1.12)	0.660	1.14 (0.73–1.78)	0.569
Histology				
SCC	-		-	
Adenocarcinoma	1.32 (0.84–2.08)	0.228	1.64 (0.97–2.79)	0.067
Other†	1.33 (0.83–2.13)	0.238	1.58 (0.91–2.75)	0.103
Tumor Size (cm)				
≤4	-		-	
>4	0.96 (0.58–1.58)	0.876	0.99 (0.46–2.11)	0.971
AJCC T stage				
T1	-		-	
T2	1.52 (0.93–2.49)	0.091	1.79 (1.05–3.05)	0.033
T3	2.05 (1.27–3.31)	0.003	2.20 (1.31–3.67)	0.003
T4	3.53 (1.44–8.65)	0.006	2.75 (1.06–7.12)	0.037
AJCC N stage				
N0	-		-	
N1	0.96 (0.62–1.50)	0.854	1.39 (0.84–2.30)	0.199
Visceral metastasis				
No	-		-	
Yes	1.95 (1.32–2.86)	<0.001	1.60 (1.03–2.49)	0.038
Treatment				
Without surgery	-		-	
With surgery	0.47 (0.29–0.76)	0.002	0.36 (0.21–0.61)	<0.001

The results were in bold if $p<0.05$.

AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, chemoradiotherapy; HR, hazards ratio; NOS, not otherwise specified; OS, overall survival; SCC, squamous cell carcinoma.

*Race–others (Asian or Pacific Islander; American Indian/Alaska Native); †Histology–others (epithelial neoplasms, NOS; transitional cell papillomas and carcinomas; cystic, mucinous and serous neoplasms; complex epithelial neoplasms; complex mixed and stromal neoplasms; unspecified neoplasms).

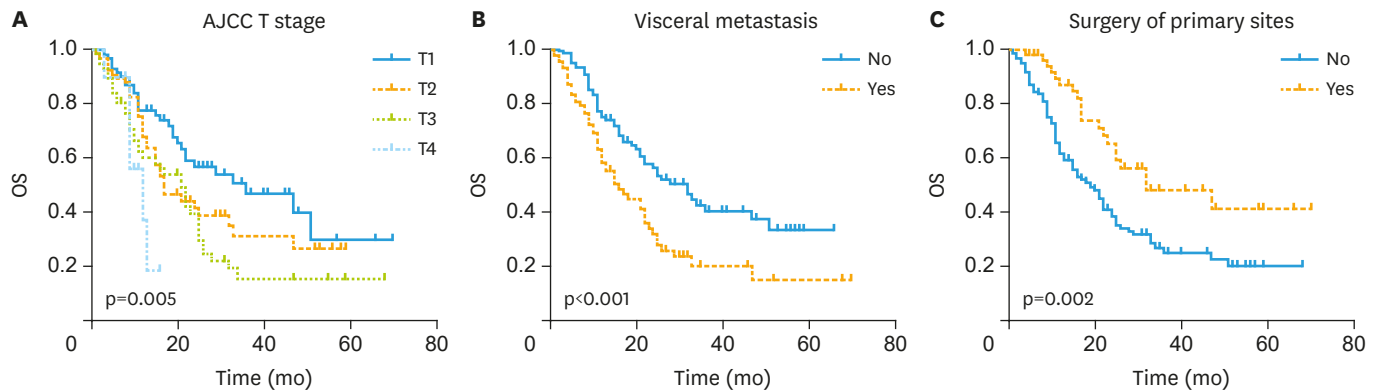


Fig. 2. Kaplan-Meier analyses with the log-rank test for OS in stage IVB cervical cancer patients receiving CRT. (A) AJCC T1 vs. T2 or T3 or T4. (B) With vs. without visceral metastasis. (C) With-surgery group vs. without-surgery group. AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; OS, overall survival.

T3, $p=0.003$, HR=2.20, 95% CI=1.31–3.67; T1 vs. T4, $p=0.037$, HR=2.75, 95% CI=1.06–7.12) and with visceral metastasis (with vs. without, $p=0.038$, HR=1.60, 95% CI=1.03–2.49) was reported as independent risk factors of OS for stage IVB cervical cancer patients receiving CRT (**Table 2, Fig. 2A and B**).

We observed superior survival benefit of surgery of primary sites ($p<0.001$, HR=0.36, 95% CI=0.21–0.61) in multivariate analysis. In detailed, the median duration was 19 months for the without-surgery group and was 32 months for with-surgery group respectively (**Fig. 2C**). The three-year survival rate was 25.3% and 48.4% for without-surgery and with-surgery group respectively. The 5-year OS rate was 20.5% and 41.5% for without-surgery and with-surgery group respectively.

3. Stratified analysis

Multiple factors may influence the treatment decision in clinical practice. To select the optimal patients amenable to surgery of primary sites, the stratified survival analysis was also investigated according to sub-classification of stage IVB cervical cancer patients. We performed the multivariate Cox regression analysis with adjusted for clinical variables including age at diagnosis, race, marital status, insurance record, grade, histology, AJCC T stage, AJCC N stage, visceral metastasis in **Table 3**. Compared with CRT alone, surgery of primary sites associated with improved OS in married patients ($p<0.001$, HR=0.20, 95% CI=0.08–0.47) with insurance ($p<0.001$, HR=0.36, 95% CI=0.20–0.63), tumor grade I–II ($p<0.001$, HR=0.12, 95% CI=0.03–0.41), adenocarcinoma ($p=0.034$, HR=0.18, 95% CI=0.04–0.88) or other histological types of cervical cancer ($p<0.001$, HR<0.01, 95% CI=0.00–0.02), tumor size no more than 4 cm ($p<0.001$, HR=0.22, 95% CI=0.11–0.46), AJCC T stage T3 ($p=0.021$, HR=0.26, 95% CI=0.09–0.81), AJCC N stage N1 ($p<0.001$, HR=0.30, 95% CI=0.16–0.56), and without visceral metastasis ($p=0.005$, HR=0.31, 95% CI=0.14–0.70).

DISCUSSION

Until now, the optimal treatment of stage IVB cervical cancer patients still remains controversial. Lack of case numbers and the diversity of clinical manifestations of stage IVB patients leads to deficiency of related researches. Thanks to SEER database, 1,144 stage IVB cervical cancer patients with treatment information were available for analysis. In this study,

Table 3. Stratified analysis for associations between surgery of primary sites and OS of stage IVB cervical cancer patients receiving CRT (matched)

Select covariates	Treatment			
	Total/death	HR	95% CI	p
Age at diagnosis				
≤50	132/68	0.32	0.15–0.68	0.003
>50	84/42	0.17	0.06–0.50	0.001
Race				
White	170/81	0.34	0.18–0.65	<0.001
Black	27/18	<0.01	4.01–448,500	0.015
Other*	19/3	-	-	0.999
Marital status				
No	94/42	0.50	0.15–1.61	0.243
Yes	107/57	0.20	0.08–0.47	<0.001
Insurance record				
No	21/12	-	-	0.998
Yes	192/96	0.36	0.20–0.63	<0.001
Grade				
I–II	92/44	0.12	0.03–0.41	<0.001
III–IV	97/55	0.47	0.22–1.02	0.056
Histology				
SCC	123/57	0.67	0.30–1.55	0.366
Adenocarcinoma	50/28	0.18	0.04–0.88	0.034
Other†	43/25	<0.01	0.00–0.02	<0.001
Tumor size (cm)				
≤4	152/72	0.22	0.11–0.46	<0.001
>4	41/20	0.89	0.18–4.41	0.888
AJCC T stage				
T1	78/30	-	-	0.997
T2	68/35	0.60	0.24–1.52	0.286
T3	60/39	0.26	0.09–0.81	0.021
T4	10/6	-	-	-
AJCC N stage				
N0	54/26	0.43	0.09–2.22	0.327
N1	156/80	0.30	0.16–0.56	<0.001
Visceral metastasis				
No	122/53	0.31	0.14–0.70	0.005
Yes				
Distant organ only	52/30	1.38	0.28–6.70	0.590
Distant LN plus organ	35/22	0.03	0.00–0.34	0.005

The results were adjusted for age at diagnosis, race, marital status, insurance record, grade, histology, AJCC T stage, AJCC N stage, visceral metastasis, and the significant results in bold, if $p < 0.05$.

AJCC, American Joint Committee on Cancer; CI, confidence interval; CRT, chemoradiotherapy; HR, hazards ratio; LN, lymph node; NOS, not otherwise specified; OS, overall survival; SCC, squamous cell carcinoma.

*Race—others (Asian or Pacific Islander; American Indian/Alaska Native); †Histology—others (epithelial neoplasms, NOS; transitional cell papillomas and carcinomas; cystic, mucinous and serous neoplasms; complex epithelial neoplasms; complex mixed and stromal neoplasms; unspecified neoplasms).

we retrospectively evaluated clinical characteristics and survival of stage IVB cervical cancer patients. The increasing AJCC T stage and visceral metastasis was reported as independent risk factors of OS for stage IVB cervical cancer patients receiving CRT. Furthermore, to our knowledge, our study first found that survival advantage significantly favors patients who underwent surgery plus CRT compared with CRT alone, revealing the important role of surgery in stage IVB cervical cancer patients.

Two types of metastasis were defined according to metastasis type of stage IVB cervical cancer patients. If the involved sites are all lymph nodes outside of the pelvis and para-aorta, the type of metastasis is designated as lymphatic metastasis; otherwise, the type of metastasis is designated as hematogenous metastasis. Specifically, patients with

hematogenous metastasis had a 5.3-fold higher risk of death than those with lymphatic metastasis [12]. In the present study, we found that stage IVB cervical cancer patients without visceral metastasis shown to have superior survival rates than those without visceral metastasis, which was consistent with previous studies [9,12-14]. Also, with increasing local tumor stage, we found that death risk increased gradually. Above all, the rationale for deeming all patients with different local tumor stage and different types of metastases as same stage IVB cervical cancer is debatable. Logically, more detailed sub-classification for stage IVB cervical cancer patients deserves further consideration in clinical practice.

According to the latest National Comprehensive Cancer Network guidelines (cervical cancer, version 2.2019), patients with metastatic cervical cancer may benefit from aggressive local therapy for oligometastatic disease include those with nodal, lung, liver or bone metastasis. The satisfied local control can be achieved either by radiotherapy or by surgery [15]. From literature review, the use of radiotherapy and multiagent chemotherapy are amenable to patients with stage IVB cervical cancer and resulted in higher survival rates [7,8]. Kim et al. [9] uncover the positive role of CRT in 24 stage IVB cervical cancer patients with lymphatic metastasis. Another study, which enrolled patients presenting with para-aortic and left supraclavicular lymph nodal metastases, recommended curative concurrent chemoradiation therapy as a feasible modality with acceptable late toxicity and high response rates [16]. Above all, CRT should be considered in patients who have only lymph node metastasis with good performance status [13]. However, the impact of surgery has not been discussed. Generally, stage IVB is considered inoperable. Despite the use of surgery being contraindicated in metastatic cervical cancer, it may be used highly personalized either for in case of particularly favorable clinical outcome or palliative intent. Promising data from studies disclose new perspectives of surgery in locally advanced cervical cancer (LACC) patients [15,17-21]. In our study, compared with CRT group, addition of surgery was inclined to prolong OS in multivariate analysis, which extended from 19 to 32 months, which offers more possibility for the treatment of stage IVB cervical cancer. The potential importance of surgery in this group of patients might be explained as follows. Although CRT can dramatically reduce the tumor burden, it can leave residual resistant cancer stem cells in the primary lesions more or less, which might turn out to be the source of uncontrolled recurrence or metastasis afterwards. Previous studies have reported the rate of residual disease on surgical specimen after CRT ranges from 32% and 59% [22-27]. Surgery contributes to eliminate the lesion, especially the chemoresistant and radioresistant stem cells, thus stops the source of further progression, which may enhance the cytotoxic effects of chemotherapy [21,28]. On the other hand, as a local treatment, surgery can effectively relieve the symptoms of bleeding, pain and excising the involved lesions of surrounding organs. This resulted in a better quality of life. Thus, surgery combined with CRT is not only useful for local control but also reduces the incidence of disease progression, which turns to longer survival.

Although surgery improves local control of neoplasia, sometimes local control of neoplasia may not translate into OS if this set of patients are accompanied with extra residual tumor. In a recent meta-analysis, Shim et al. [29] reported that adjuvant hysterectomy indeed did not improve survival in patients with LACC. Furthermore, in a phase II clinical trial, for LACC patients, radiotherapy-chemotherapy followed by surgery with intraoperative radiation therapy in LACC patients seems to be effective only for patients with pathological complete response to treatment or partial response with residual tumor limited to the cervix. Houvenaeghel et al. [24] reported that adjuvant surgery could improve the outcome of patients with bulky residual tumor (≥ 2 cm) after CRT for LACC. Therefore, surgery should be contraindicated for some sub-group patients. Patients with visceral metastasis

may not benefit from surgery. Perhaps, patients may undergo surgery of metastatic sites simultaneously when diagnosed with oligometastatic disease [30]. Besides, surgery may be done with caution to patients with advanced tumor grade (II–IV), larger tumor size (more than 4 cm) and no regional lymph node metastasis.

In addition, we must acknowledge some limitations in this study. First, due to the retrospective nature of this study, some biases were inevitable in spite of some advanced statistical methods were applied. Future randomized controlled trials are desperately in need. Besides, the study was conducted with a highly selected population. Patients who received either chemotherapy or radiotherapy, accounting for 33% (923/2,733) of the whole stage IVB cervical cancer population, were excluded from the analysis. Patients with stage IVB cervical cancer is a very heterogeneous population regarding the primary tumor well as the location and number of distant metastasis. The disease spread pattern is the major determinant when deciding which treatment be applied primarily. This is a major limitation of our study. We also excluded some surgical procedures which can be regarded diagnostic including LEEP, local tumor excision, and simple hysterectomy. However, it did not assure that the surgery was not diagnostic. This is another factor that could cause selection bias. Second, detailed information regarding the treatment information and surgical morbidity was not available from SEER database. We did not know either the administration method of chemotherapeutic drugs (including dose, cycles, and regimens, etc) and radiation or the sequence of chemotherapy, radiotherapy and surgery. This is another a major limitation of our study which can affect the results. Additional hysterectomy following radiation is a controversial issue even in locally advanced cervical cancer without distant metastasis. A recent randomized clinical trial reported that post-radiation hysterectomy had no therapeutic impact [31]. Future analysis should specify different treatment modalities to elucidate the true significance of surgery in stage IVB cervical cancer patients. Also, the lack of information about any imaging investigation performed before surgery to check the treatment response was another limitation. If imaging had been performed, we could know whether patients with stable or progressive disease were excluded as surgical candidates. Moreover, more detailed surgery information such as residue tumors, surgical complications or the quality of life after surgery should also be weighted in subsequent studies in case of the increased risk of adverse effect in patients. Finally, there are limited data about the outcome of patients treated with curative surgery (including surgery of primary sites and surgery of metastatic sites). For patients with oligo metastasis, it remains elusive whether curative surgery combined with CRT improves OS or not. Nevertheless, this is the first paper discussing the clinical characteristics and the effect of surgery in stage IVB cervical cancer patients, which might provide some guide in our clinical practice.

In conclusion, surgery combined with CRT may be used to achieve longer survival in patients with stage IVB cervical cancer patients. However, it deserves large scale prospective clinical trials to confirm.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline demographic and clinicopathological characteristics of stage IVB cervical cancer receiving CRT

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Supplementary Fig. 1

The detailed information of surgery procedure of primary sites.

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