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Original Article

Different surgical methods for FIGO stage IVB cervical cancer patients receiving chemotherapy: a population-based study

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ABSTRACT

Objective: To assess survival differences between non-extensive surgery (NES) and extensive surgery (ES) in International Federation of Gynecology and Obstetrics (FIGO) stage IVB cervical cancer patients receiving chemotherapy from a population-based database, the Surveillance, Epidemiology and End Results.
Methods: Propensity matching was conducted to minimize heterogeneity. Survival analysis was performed by the Kaplan–Meier method, log-rank test, and Cox proportional hazards model.
Results: A total of 154 patients met screening criteria, among whom 84 patients (84/154) underwent NES while 70 patients (70/154) underwent ES. After matching, no survival advantage was observed in ES group compared with NES group (p=0.066; hazard ratio [HR]=1.54; 95% confidence interval [CI]=0.97–2.42). Stratified analyses suggested ES prolonged overall survival in patients with histology other than squamous cell carcinoma and adenocarcinoma (p=0.028; HR=0.36; 95% CI=0.15–0.89) and American Joint Committee on Cancer (AJCC) T stage T1 (p=0.009; HR=0.18; 95% CI=0.05–0.66). Despite no survival benefit after regional lymph node surgery (p=0.629; HR=0.88; 95% CI=0.53–1.47), subgroup analyses demonstrated that patients younger than 50 (p=0.006; HR=0.21; 95% CI=0.07–0.64), with AJCC T stage T1 (p=0.002; HR=0.09; 95% CI=0.02–0.42), T3 (p=0.001; HR=0.02; 95% CI=0.00–0.21), hematogenous metastasis (p=0.036; HR=0.27; 95% CI=0.08–0.92) and without surgery of other sites (p=0.040; HR=0.01; 95% CI=0.00–0.79) might achieve longer survival after regional lymph node surgery.
Conclusion: In conclusion, ES or regional lymph node surgery may provide survival advantage for certain subgroup of FIGO IVB cervical cancer patients receiving chemotherapy. However, it deserves large scale prospective clinical trials to confirm.

Keywords: Surgery Methods; FIGO Stage IVB Cervical Cancer; Overall Survival

Synopsis

Extensive surgery or regional lymph node surgery may provide survival advantage for certain subgroup of International Federation of Gynecology and Obstetrics IVB cervical cancer patients receiving chemotherapy.

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

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

INTRODUCTION

Cervical cancer ranked as fourth most prevalent and fourth leading lethal malignancy in women worldwide, with nearly 604,000 new cases and 342,000 deaths in 2020 [1,2]. According to the National Comprehensive Cancer Network (NCCN) guidelines, the primary treatment of early-stage cervical cancer is either surgery or radiotherapy. 80% of women with early-stage disease (stage I–II) and 60% of women with stage III disease can be cured with effective treatment (including surgery and concurrent chemoradiotherapy) [3]. Nevertheless, patients who develop distant metastases (International Federation of Gynecology and Obstetrics [FIGO] stage IVB) are rarely curable, with 5-year survival rate less than 20%. Even worse, approximately 50% of these patients show a fatal outcome within 1 year [4,5].

Currently, there are no standard treatment guidelines being established for stage IVB cervical cancer compared with locally advanced cervical cancer. According to the latest NCCN guideline, palliative therapy including platinum-based systemic chemotherapy, the angiogenesis inhibitor bevacizumab and immunotherapy listed as treatment choice for metastatic cervical cancer patients [6]. However, systemic therapy alone is usually insufficient to control local disease progression in the primary tumor, including pain, bleeding, secretions, and invasion of adjacent organs [7,8]. In these situations, locoregional therapy may be considered for control of pelvic disease and other symptoms [9-11]. Moreover, locoregional radiotherapy combined with systemic chemotherapy would prolong survival of metastatic cervical cancer patients [6]. Under current guidelines, surgery is generally not recommended for advanced cervical cancer patients. However, certain studies have shown that primary tumor resection tends to improve survival outcomes for primary metastatic cervical cancer patients [5,6,12]. Therefore, in addition to radiotherapy, surgery might be considered as another effective approach mitigating the effects of local disease progression. Surgical method for removing primary lesions mainly included total hysterectomy, extended hysterectomy, radical hysterectomy and pelvic exenteration [13]. Among these studies, few researchers focused on investigating the relationship between different surgical methods and clinical outcomes in FIGO stage IVB cervical cancer patients.

In the present study, we retrieved detailed clinicopathologic and treatment information of initially diagnosed stage IVB cervical cancer patients who received surgical treatment and chemotherapy from the Surveillance, Epidemiology and End Results [SEER] database. After matching, we divided patients into 2 groups: non-extensive surgery (NES) group (including total hysterectomy [simple, pan-] with or without removal of tubes and/or ovary) and extensive surgery (ES) group (including modified radical or extended hysterectomy, radical hysterectomy and extended radical hysterectomy). We evaluated survival outcomes in the above 2 groups, 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 [14]. The National Cancer Institute's SEER*Stat software (version 8.3.5; Surveillance Research Program, National Cancer Institute SEER*Stat software, https://seer.cancer.gov/) 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

The retrospective clinical data of stage IVB cervical cancer patients from 2010–2019 was retrieved from the recent SEER-18 database. Due to loss of detailed information about site-specific metastasis before 2010, we limited this study to patients diagnosed between 2010 and 2019. 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. The following baseline demographic and clinicopathologic characteristics of patients were collected: age at diagnosis; year of diagnosis, between 2010–2019; race, White, Black or others including Asian or Pacific Islander; American Indian/Alaska Native; marital status, married or unmarried; 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 including 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; tumor size; American Joint Committee on Cancer (AJCC) stage; metastasis type, lymphatic metastasis or hematogenous metastasis; cause-specific death classification; vital status; survival months.

In addition, treatment data were retrieved for each case included chemotherapy, radiotherapy and surgery (including primary sites, regional lymph node and other sites). Only patients who underwent chemotherapy were included in this study. According to the operation choice of primary sites, patients were classified into 2 groups in our final analysis including NES group and ES group. NES group includes total hysterectomy removes both the corpus and the cervix uteri and may also include a portion of vaginal cuff with or without removal of tubes and/or ovary, and ES group includes modified radical or extended hysterectomy, radical hysterectomy and extended radical hysterectomy. Surgery of other sites is the surgical removal of distant lymph nodes or other tissues or organs beyond the primary site.

3. Statistical analysis

Data analysis was executed using R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). The risk factors of different type of surgery data were evaluated by Kaplan-Meier method. Propensity matching was performed using the nearest neighbor matching to reduce the effect of confounding factors such as age at diagnosis, race, marital status, grade, histology, tumor size, AJCC stage T, AJCC stage N, metastasis type. The primary outcome of the survival analysis was the overall survival (OS), which was defined from the time of diagnosis of uterine cervical cancer to causes of cancer-specific of death. Estimate of OS was performed using the Kaplan-Meier method and the log-rank test. The survival curves were made by Graph Pad Prism. Stratified analysis was applied to estimate associations between different surgical methods and survival of FIGO stage IVB patients receiving chemotherapy. A probability value of less than 0.05 was considered statistically significantly different.

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RESULTS

1. Patients' characteristics

The screening flow-chart was shown in **Fig. 1.** Between 2010 and 2019, a total of 2611 patients with FIGO stage IVB cervical cancer were identified from the SEER database. Patients with one more primary malignant tumor (n=358), no evidence of primary tumor (n=9) and clinical diagnosis only or direct visualization without microscopic confirmation (n=14) were excluded from this study. In addition, patients died of other causes (n=139), with survival months of 0 (n=143) or unknown survival months (n=2) were also filtered out. In terms of specific surgery procedure, unknown type of surgery (n=1,751) and patients without chemotherapy (n=31) were excluded. Following the screening procedure, a number of 154 cervical cancer patients were finally included in this study, among whom 84 patients (84/154, 54.5%) treated

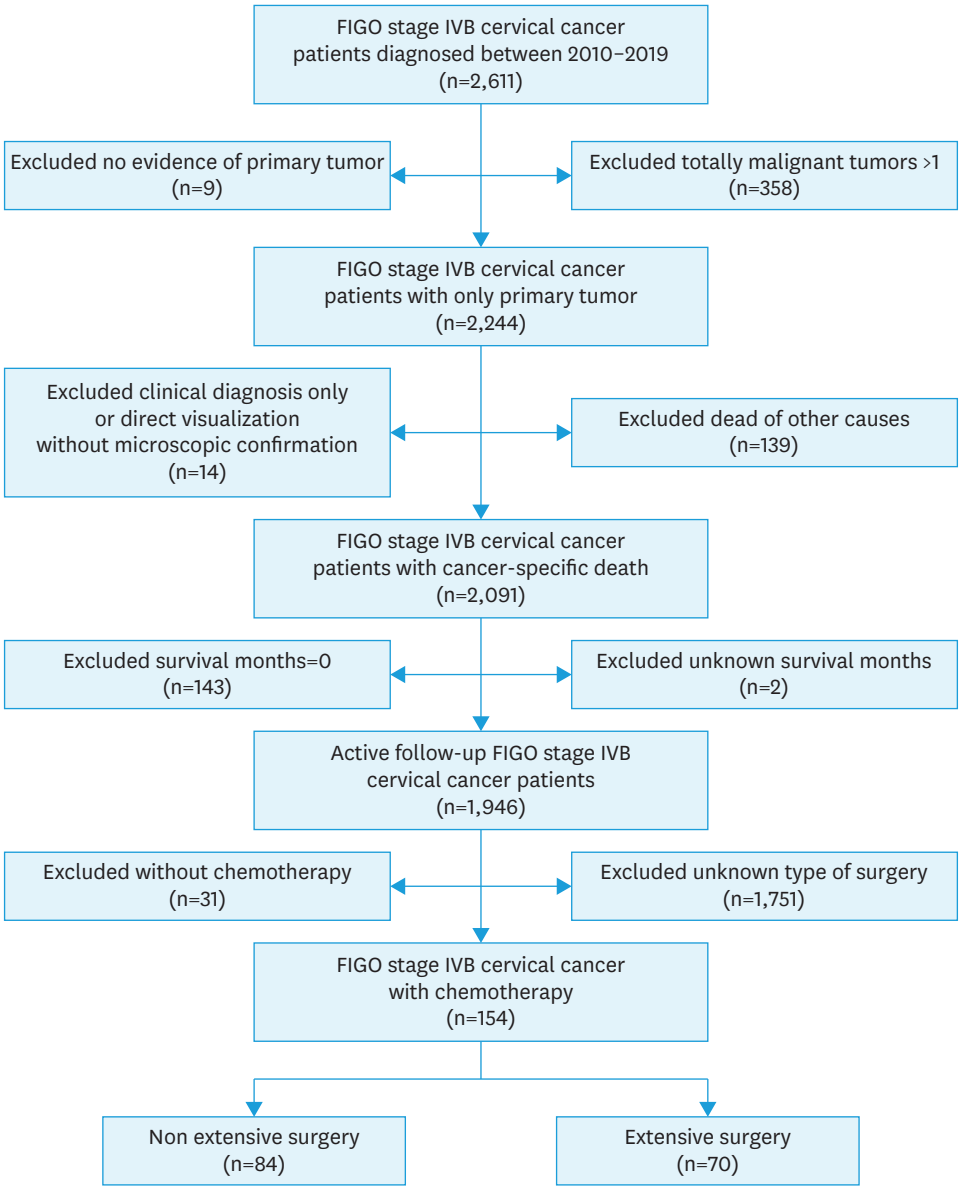

Fig. 1. The flowchart of this study.
FIGO, International Federation of Gynecology and Obstetrics.

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with NES while 70 patients (70/154, 45.5%) treated with ES. And 48 (48/153, 31.4%) patients underwent lymph node surgery while 105 (105/153, 68.6%) patients did not; 115 (115/154, 74.7%) patients underwent surgery of other sites and 39 (39/154, 25.3%) patients did not. However, there were statistically significant differences among different type of surgery in grade (p=0.012) and AJCC N (p=0.047) (**Table S1**).

To make each group comparable, via the methodology of matching, we then intended to balance the discrepancy of prognostic factors between the 2 groups. After matching with ratio 1:1, 70 patients were kept in each group and no notable difference between the NES and ES group was observed. Detailed information of clinical characteristics in the 2 groups was shown in **Table 1**.

Table 1. Baseline demographic and clinicopathologic characteristics of different surgery methods in FIGO stage IVB cervical cancer patients receiving chemotherapy (matched)

Characteristics	NES (n=70)	ES (n=70)	p-value
Age at diagnosis			0.735
<50	32 (45.7)	35 (50.0)	
≥50	38 (54.3)	35 (50.0)	
Race			0.490
White	57 (81.4)	62 (88.6)	
Black	7 (10.0)	4 (5.7)	
Others*	6 (8.6)	4 (5.7)	
Marital status			0.453
Unmarried	30 (42.9)	26 (37.1)	
Married	38 (54.3)	39 (55.7)	
Unknown	2 (2.9)	5 (7.1)	
Grade			0.059
I–II	24 (34.3)	25 (35.7)	
III–IV	33 (47.1)	41 (58.6)	
Unknown	13 (18.6)	4 (5.7)	
Histology			0.608
SCC	28 (40.0)	29 (41.4)	
Adenocarcinoma	26 (37.1)	21 (30.0)	
Other†	16 (22.9)	20 (28.6)	
Tumor size			0.701
≤2 cm	6 (8.6)	5 (7.1)	
>2 cm, ≤4 cm	15 (21.4)	12 (17.1)	
>4 cm	29 (41.4)	36 (51.4)	
Unknown	20 (28.6)	17 (24.3)	
AJCC T			0.488
T1	22 (31.4)	21 (30.0)	
T2	20 (28.6)	24 (34.3)	
T3	20 (28.6)	16 (22.9)	
T4	6 (8.6)	9 (12.9)	
Unknown	2 (2.9)	0 (0.0)	
AJCC N			0.176
N0	26 (37.1)	20 (28.6)	
N1	42 (60.0)	50 (71.4)	
Unknown	2 (2.9)	0 (0.0)	
Metastasis type			0.265
Lymphatic metastasis	21 (30.0)	30 (42.9)	
Hematogenous metastasis	35 (50.0)	27 (38.6)	
Others‡	14 (20.0)	13 (18.6)	

Values are presented as number (%).
AJCC, American Joint Committee on Cancer; ES, extensive surgery; FIGO, International Federation of Gynecology and Obstetrics; NES, non-extensive surgery; NOS, not otherwise specified; 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).
‡Metastasis type--others (lymphatic metastasis and hematogenous metastasis; distant metastasis, NOS).

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2. Survival analysis

Next, we performed survival analysis to investigate the role of different surgical method in patients' survival. The median survival month of patients who underwent NES and ES was 51.5 and 31 months, respectively. The 3-year and 5-year survival rates of NES group was 40% and 31%, respectively, while the 3-year and 5-year survival rates of ES group was 33% and 23%, respectively. We observed noninferior survival impact of ES both in univariate (p=0.066; hazard ratio [HR]=1.54; 95% confidence interval [CI]=0.97–2.42) and multivariate Cox regression analysis (p=0.094; HR=1.56; 95% CI=0.93–2.64) (**Table 2**, **Fig. 2A**).

In addition to the removal of the primary lesion, for FIGO stage IVB cervical cancer patients, surgical procedure was also comprised of the removal of regional lymph nodes and other sites including the surgical removal of distant lymph node or other tissue or organ beyond the primary site. The median survival month of patients with or without regional lymph nodes surgery was 41.5 and 30 months, respectively. The 3-year and 5-year survival rates of patients with regional lymph nodes surgery was 55% and 41%, respectively, while the 3-year and 5-year survival rates patients without regional lymph nodes surgery was 18% and 12%, respectively. And the median survival month of patients with or without other sites surgery was 44.5 and 41.5 months, respectively. The 3-year and 5-year survival rates of patients with other sites surgery was 53% and 38%, respectively, while the 3-year and 5-year survival rates patients without other sites surgery was 20% and 16%, respectively. Still, we found that no survival

Table 2. Survival analysis of different surgery methods in FIGO stage IVB cervical cancer patients receiving chemotherapy (matched)

Characteristics	Survival months (median)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Surgery of primary site					
NES	51.5	1.00		1.00	
ES	31	1.54 (0.97–2.42)	0.066	1.56 (0.93–2.64)	0.094
Regional lymph node surgery					
No	30	1.00		1.00	
Yes	41.5	0.88 (0.53–1.47)	0.629	1.01 (0.56–1.82)	0.976
Surgery of other sites					
No	41.5	1.00		1.00	
Yes	44.5	1.01 (0.62–1.66)	0.963	1.12 (0.64–1.94)	0.699

The multivariate results were adjusted for age at diagnosis, race, marital status, grade, histology, tumor size, AJCC T, AJCC N, metastasis type, radiotherapy.
AJCC, American Joint Committee on Cancer; CI, confidence interval; ES, extensive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazards ratio; NES, non-extensive surgery.

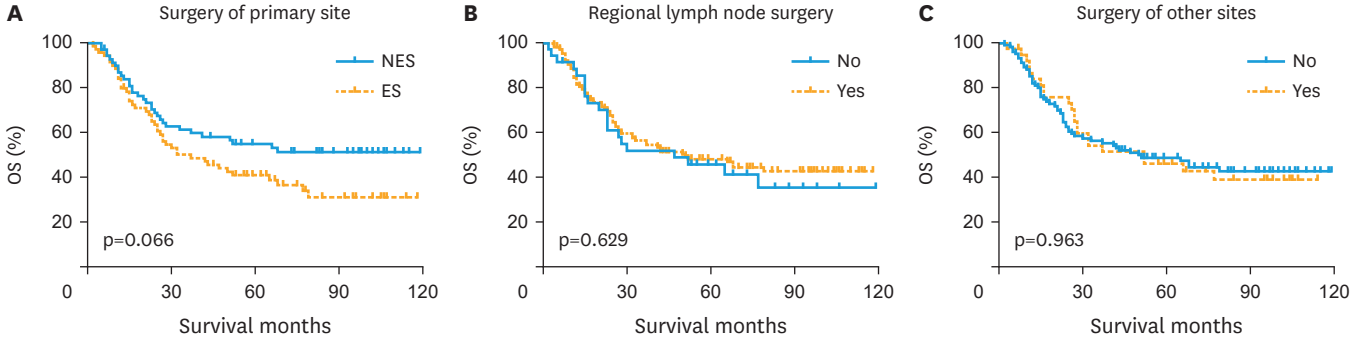

Fig. 2. Kaplan-Meier analyses with the log-rank for OS in FIGO stage IVB cervical cancer patients receiving chemotherapy. (A) NES vs. ES. (B) with vs. without regional lymph node surgery. (C) with vs. without surgery of other sites.
ES, extensive surgery; FIGO, International Federation of Gynecology and Obstetrics; NES, non-extensive surgery; OS, overall survival.

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benefit of regional lymph node surgery (p=0.629; HR=0.88; 95% CI=0.53–1.47) and surgical procedure of other sites (p=0.963; HR=1.01; 95% CI=0.62–1.66) (**Table 2**, **Fig. 2B and C**).

3. Stratified analysis

In clinical practice, comprehensive consideration is needed when making treatment decisions. To select the optimal patients amenable to different type of surgery, the stratified survival analyses were also conducted according to sub-classification of FIGO stage IVB cervical cancer patients receiving chemotherapy. The multivariate Cox regression analysis results with adjusting for variants including age at diagnosis, race, marital status, grade, histology, tumor size, AJCC T, AJCC N, metastasis type, regional lymph node surgery, surgery of other sites and radiotherapy were shown in **Table 3**.

Compared with NES group, ES associated with improved OS in patients with histology other than squamous cell carcinoma and adenocarcinoma (p=0.028, HR=0.36; 95% CI=0.15–0.89) and AJCC T stage T1 (p=0.009; HR=0.18; 95% CI=0.05–0.66). In contrast, for patients younger than 50 (p=0.021; HR=3.36; 95% CI=1.21–10.85), grade I–II (p=0.026; HR=12.83; 95% CI=1.36–121.24), AJCC T stage T3 (p<0.001; HR=27.68; 95% CI=5.04–152.16), lymphatic metastasis (p=0.015; HR=4.75; 95% CI=1.36–16.62), histology diagnosed with squamous cell carcinoma (p=0.043; HR=3.42; 95% CI=1.04–11.25) or without regional lymph node resection (p=0.004; HR=46.90; 95% CI=3.39–649.31), ES shortened their OS.

We also performed stratified analysis to identify subgroup patients who would benefit from regional lymph node surgery. Patients who underwent regional lymph node surgery achieved long survival in patients younger than 50 (p=0.006; HR=0.21; 95% CI=0.07–0.64), AJCC T stage T1 (p=0.002; HR=0.09; 95% CI=0.02–0.42), AJCC T stage T3 (p=0.001; HR=0.02; 95% CI=0.00–0.21), hematogenous metastasis (p=0.036; HR=0.27; 95% CI=0.08–0.92) and without surgery of other sites (p=0.040; HR=0.01; 95% CI=0.00–0.79) compared with those who did not (**Table 4**).

DISCUSSION

Cervical cancer patients who develop distant metastases manifested with dismal clinical outcomes, with 5-year survival rate less than 20% [4,5]. According to NCCN guidelines, the preferred first-line treatment for FIGO stage IVB cervical cancer patients includes platinum-based chemotherapy combined with bevacizumab [15]. However, systemic therapy is necessary for systemic tumor control but exhibited limited efficacy in treating localized tumors. Local control of the primary tumor plays an important role in the survival outcomes of many cancers such as esophageal, renal cell, bladder and prostate carcinoma [16-20]. Locoregional radiotherapy is used selectively in FIGO stage IVB cervical cancer patients to assuage the high burden of pelvic disease in clinical practice [21,22]. Surgery was recommended as another way to diminish primary tumor load. Recently, in spite of the controversial clinical efficacy of primary tumor resection for stage IVB cervical cancer, increasing retrospective studies confirmed that surgery could improve the OS [6,8,12,23,24]. Our previous research also underlined the critical role of surgery in comparison with chemoradiotherapy [5]. Although these studies demonstrated the benefits of surgery in patients with stage IVB cervical cancer, to our knowledge there were few published studies comparing different surgical methods in patients with FIGO stage IVB cervical cancer.

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Table 3. Stratification analysis for associations between different surgery methods of primary site and survival of FIGO stage IVB patients receiving chemotherapy (matched)

Select covariates	Number/event		Overall survival	
	NES	ES	HR (95% CI)	p-value
Age at diagnosis				
<50	32/14	35/21	3.63 (1.21–10.85)	**0.021**
≥50	38/18	35/23	1.62(0.73–3.60)	0.234
Race				
White	56/26	62/37	1.45 (0.81–2.62)	0.214
Black	7/4	4/3		
Others*	6/2	4/4		
Marital status				
Unmarried	30/15	26/15	0.85 (0.24–2.98)	0.799
Married	38/16	39/25	2.34 (0.99–5.48)	0.051
Grade				
I–II	25/6	25/14	12.83 (1.36–121.24)	**0.026**
III–IV	33/21	41/27	1.51 (0.74–3.07)	0.259
Histology				
SCC	26/13	29/19	3.42 (1.04–11.25)	**0.043**
Adenocarcinoma	25/9	21/14	0.90 (0.20–4.14)	0.897
Other†	18/10	20/11	0.36 (0.15–0.89)	**0.028**
Tumor size				
≤2 cm	7/1	5/1		
>2 cm, ≤4 cm	15/8	12/5		
>4 cm	29/13	36/22	2.47 (0.96–6.35)	0.060
AJCC T				
T1	23/6	21/6	0.18 (0.05–0.66)	**0.009**
T2	19/12	24/17	1.94 (0.52–7.15)	0.321
T3	20/12	16/14	27.68 (5.04–152.16)	**<0.001**
T4	6/2	9/7		
AJCC N				
N0	25/13	20/12	1.71 (0.23–12.89)	0.601
N1	42/19	50/32	1.50 (0.72–3.09)	0.277
Metastasis type				
Lymphatic metastasis	20/6	30/17	4.75 (1.36–16.62)	**0.015**
Hematogenous metastasis	34/17	27/18	1.85 (0.72–4.75)	0.201
Regional lymph node surgery				
No	21/8	14/12	46.90 (3.39–649.31)	**0.004**
Yes	47/24	56/32	1.50 (0.80–2.85)	0.209
Surgery of other sites‡				
No	56/25	45/29	1.83 (0.94–3.56)	0.074
Yes	13/7	25/15	6.20 (0.80–48.14)	0.081
Radiotherapy				
No§	24/15	23/18	1.64 (0.50–5.37)	0.415
Yes	45/17	47/26	1.95 (0.90–4.22)	0.092

The results were in bold if $p<0.05$.
AJCC, American Joint Committee on Cancer; CI, confidence interval; ES, extensive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazards ratio; NES, non-extensive surgery; NOS, not otherwise specified; 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).
‡Surgery of other sites--the surgical removal of distant lymph node(s) or other tissue(s) or organ(s) beyond the primary site.
§Radiotherapy--no (none or unknown).

Our study was a preliminary study which may attest to the role of ES in metastatic cervical cancer patients. We used public databases to search for relevant medical cases, 154 FIGO stage IVB cervical cancer patients with chemotherapy from the SEER database were available for analysis. We retrospectively evaluated the impact of different surgical type on survival. As a result, in all patients, ES did not translate into survival benefit compared with less ES.

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Table 4. Stratification analysis for associations between regional lymph node surgery and survival of FIGO stage IVB patients receiving chemotherapy (matched)

Select covariates	Number/event		Overall survival	
	No	Yes	HR (95% CI)	p-value
Age at diagnosis				
<50	18/11	48/24	0.21 (0.07–0.64)	**0.006**
≥50	17/9	56/32	2.06 (0.76–5.55)	0.151
Race				
White	27/17	91/47	0.67 (0.34–1.35)	0.262
Black	5/2	6/5		
Others*	3/3	7/4		
Marital status				
Unmarried	13/8	41/24	2.09 (0.58–7.54)	0.258
Married	20/13	58/28	0.45 (0.18–1.12)	0.085
Grade				
I–II	15/7	34/13	0.11 (0.01–1.10)	0.061
III–IV	17/12	57/36	1.07 (0.42–2.71)	0.883
Histology				
SCC	15/9	40/25	1.16 (0.33–4.07)	0.812
Adenocarcinoma	14/8	33/15	0.58 (0.05–6.30)	0.651
Other†	6/5	31/16	0.34 (0.11–1.09)	0.070
Tumor size				
≤2 cm	6/3	6/0		
>2 cm, ≤4 cm	4/1	24/12		
>4 cm	11/7	51/28	1.36 (0.35–5.37)	0.659
AJCC T				
T1	8/3	35/9	0.09 (0.02–0.42)	**0.002**
T2	10/7	33/23	4.55 (0.80–25.77)	0.087
T3	8/7	28/20	0.02 (0.00–0.21)	**0.001**
T4	8/5	7/4		
AJCC N				
N0	19/11	29/15	0.38 (0.08–1.92)	0.243
N1	14/11	75/41	1.17 (0.49–2.84)	0.721
Metastasis type				
Lymphatic metastasis	8/6	41/18	2.52 (0.40–15.93)	0.325
Hematogenous metastasis	18/12	44/24	0.27 (0.08–0.92)	**0.036**
Surgery of primary site				
NES	21/10	48/24	1.80 (0.61–5.34)	0.290
ES	14/12	56/32	0.62 (0.25–1.52)	0.293
Surgery of other sites‡				
No	25/14	75/41	1.18 (0.54–2.58)	0.672
Yes	10/8	29/15	0.01 (0.00–0.79)	**0.040**
Radiotherapy				
No§	15/12	34/21	0.70 (0.19–2.61)	0.601
Yes	20/10	70/35	1.77 (0.72–4.35)	0.211

The results were in bold if p<0.05.
AJCC, American Joint Committee on Cancer; CI, confidence interval; ES, extensive surgery; FIGO, International Federation of Gynecology and Obstetrics; HR, hazards ratio; NES, non-extensive surgery; NOS, not otherwise specified; 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).
‡Surgery of other sites--the surgical removal of distant lymph node(s) or other tissue(s) or organ(s) beyond the primary site.
§Radiotherapy--no (none or unknown).

As we all known, radical hysterectomy is the most classical surgical procedure for operable cervical cancer patients. The core of radical hysterectomy lies in extensive hysterectomy (cutting off the main and sacral ligaments and other uterine tissues near the pelvic wall, and removing 1/4–1/3 of the upper vaginal segment), in order to ensure complete removal of the cervix and uterine body and achieve a negative cutting edge. Traditionally, radical

hysterectomy is preferred as the standard of care for most early-stage cervical cancers. However, for primary metastatic cervical cancer, the treatment aim was rather prolonging the OS than cure. The necessities of ES for IVB stage IVB cervical cancer with low life expectancy seemed elusive. Therefore, accepting NES seemed more reasonable compared with ES. Next, we performed subgroup analysis stratified by clinical characteristics and various treatment options. Nevertheless, not all subgroup patients achieve the same clinical outcome of NES and ES. In our study, radical surgery may be done with caution to patients younger than 50, with histologically diagnosed squamous carcinoma, with grade I–II, with AJCC T stage T3, with lymphatic metastasis or without regional lymphadenectomy. For these patients, the elevated HR value when performing ES may be attributed to the intraoperative complications such as bleeding, ureteral and bladder injuries, as well as postoperative complications such as fistula, urinary retention or incontinence, and sexual dysfunction. Unfortunately, we could not get access to more detailed surgery information such as surgical complications or the quality of life after surgery. Further studies were needed to validate its value in different subgroup patients.

Pelvic lymphadenectomy is recognized as a standard of care for cervical cancer patients over centuries. Yet, for metastatic cervical cancer patients, whether lymphadenectomy was effective or not remained to be explored. For stage IVB cervical cancer patients, previous studies categorized them into hematogenous metastasis or lymphatic metastasis. Surprisingly, we found that regional lymph node surgery benefited patients with hematogenous metastasis but not with lymphatic metastasis. Indeed, accompanied with distant lymph node metastasis, removing reginal lymph nodes appeared to be futile and meaningless. After all, for end stage tumor patients, lymphadenectomy was an unnecessary and morbid procedure that put them at an increased risk for the development of chronic lower-extremity lymphedema after surgery [25]. However, for patients with hematogenous metastasis, we speculated that lymphadenectomy might be a potential way to block lymphatic metastatic pathway, which may contribute to prolonging the survival of patients. Besides, when come to patients with AJCC T stage T3 and patients who underwent surgery of other sites including the surgical removal of distant lymph nodes or other tissues or organs beyond the primary site, regional lymph node surgery was also recommended. In our research, it was well worth noting that both extensive hysterectomy and regional lymphadenectomy was associated with improved survival for patients with tumor confined to the uterus (AJCC T stage T1). The primary lesion of this subgroup patients was not severe but manifested with distant metastasis. Generally, they were considered inoperable. Our results provided a novel treatment modality for pursuing favorable clinical outcome. Perhaps, while systemic symptoms were controlled by chemotherapy, patients may benefit from ES and lymph node dissection.

Moreover, previous literature review suggested surgery of metastatic sites is viable and beneficial for survival in certain circumstances. For instance, as for cervical carcinoma metastatic to the lungs, surgery combined with chemotherapy (plus radiation therapy [RT] for stage IVB) is able to provide a better prognosis for large solitary pulmonary metastatic tumors. Coincidentally, regarding cervical cancer metastatic to the brain, craniotomy is promising combined with RT for solitary brain metastases [26]. However, in our study, we did not observe a survival benefit of the surgical removal of distant lymph nodes or other tissues or organs beyond the primary site. The result was due to amounts of reasons including the highly selective patients, the number of metastatic sites, whether primary tumor was controlled or not, different state of patients and so on.

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We must admit that there were some limitations in this study. First of all, as its retrospective nature, it was inevitable that there existed some bias in spite of advanced statistical methods were applied. In addition, the cases included in this study were strictly screened, and a large number of patients were excluded from the analysis, resulting in selection bias. Especially, patients with no chemotherapy or unknown chemotherapeutic information, accounting for 31% (812/2,611) of the whole stage IVB cervical cancer population were excluded from the analysis. Second, the lack of detailed treatment information in cervical cancer patients, including chemotherapeutic drugs (including dose, cycles, and regimens, etc.), radiation (including definitive radiotherapy or palliative radiotherapy), the sequence of treatment modalities, or administration with or without target therapy (including bevacizumab, etc.) and immunotherapy (including pembrolizumab, etc.), should be incorporated in analysis. Also, 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. Besides, the information about any imaging evaluation of the chemotherapeutic response before surgery was essential. If radiological examination was available, we could further evaluate the applicability of surgery even different surgical methods for patients with regressive, stable or progressive disease. This is a major limitation of our study. Finally, there are limited data about the outcome of patients treated with curative surgery (including surgery of primary sites, surgery of regional lymph node and surgery of metastatic sites). For patients with oligo metastasis, it remains elusive whether curative surgery improves OS or not. Nevertheless, this is the first paper discussing the impact of different surgical methods on survival of stage IVB cervical cancer patients, which might provide some clues in our clinical practice. Due to the limited number of patients, larger sample sizes and prospective further studies are needed for more comprehensive and comparative analyses.

In conclusion, our study found that ES and regional lymph node surgery did not provide significantly improved survival for FIGO stage IVB cervical cancer patients except for patients with tumor confined to the uterus. More researches were desperately in need to verify our conclusion and make more appropriate treatment plans, so as to prolong the survival time and improve the quality of life of such patients.

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SUPPLEMENTARY MATERIAL

Table S1

Baseline demographic and clinicopathologic characteristics of different surgery methods in FIGO stage IVB cervical cancer patients receiving chemotherapy

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