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Clinical significance of intensity-modulated radiotherapy (IMRT) to the distant metastatic lymph nodes for metastatic cervical cancer

Chi Fang[1†], Suping Liu[1†], Jie Xia[2†], Xiaohua Wu[1*], Jun Zhu[1*] and Guihao Ke[1*]

Abstract

Objective To retrospectively explore the clinical significance of radiotherapy to the distant metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) in metastatic cervical cancer. Hereinto, these cervicothoracic lymph nodes were metastasized from IB1-IVA (initial stage at first treatment), and IVB initially had metastatic disease in these areas at diagnosis.

Methods Metastatic cervical cancer only with the distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.), without distant parenchymal organs metastasis such as lung, liver, bone, and peritoneum, were enrolled in the analysis. These patients were classified into IB1-IVA and IVB based on their initial stage of first treatment. All patients received IMRT for the distant metastatic lymph nodes. The progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan–Meier method.

Results Overall, the median PFS was 9 months, and the median OS was 27 months. The subgroup analysis showed that for IB1-IVA, the median PFS was 11 months, and the median OS was 30.5 months. For IVB, the median PFS was 8 months, and the median OS was 16 months.

Conclusion Radiotherapy is beneficial to the distant metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.), and could effectively bring the longer PFS and OS for metastatic cervical cancer.

Keywords Cervical cancer, Intensity-modulated radiotherapy, Distant metastatic lymph nodes, Survival

Introduction

Cervical cancer (CC) is one of the most known malignancies and ranks fourth in both morbidity and mortality in gynecologic tumors worldwide [1]. More than 85% of cervical cancer occurs in developing countries, and has a much higher mortality in developing than in developed countries [2]. Moreover, China almost accounts for 11.9% of global cervical cancer deaths due to its large population [3], accompanied by the increasing incidence annually.

So far, radiotherapy has been widely used for cervical cancer treatment and brought the improvements in overall survival (OS) and disease-free survival with the

†Chi Fang, Suping Liu and Jie Xia contributed equally to this work.

*Correspondence:
Xiaohua Wu
wu.xh@fudan.edu.cn
Jun Zhu
dragonzld@163.com
Guihao Ke
kegh5734@126.com
[1]Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, 270 Dong-An Road, Shanghai 200032, China
[2]Department of Digestive Endoscopic Center, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

radiotherapy advancements [4]. However, recurrent and metastatic cervical cancer remain quite poor therapeutic outcomes to date, despite the fact that early-stage and locally advanced patients could be successfully managed with radical operation and chemoradiotherapy [5]. Overall survival (OS) for recurrent and metastatic cervical cancer is reported to be only 13.3 months [6]. The median post-recurrence survival (PRS) of the recurrent patients is 16.4–18 months [7, 8]. Actually, the recurrent and metastatic cervical cancer after platinum-based chemoradiotherapy has minimal treatment options in the clinic. There is even no standard treatment for metastatic cervical cancer because of heterogeneous manifestations. The guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society of Gynecological Oncology (ESGO) both recommend palliative chemotherapy as the standard treatment for recurrent and metastatic cervical cancer [9, 10]. However, the reported response rate is at a shallow level at 15–30%, and the response duration is also quite short in recurrent and metastatic cervical cancer [6, 11]. Indeed, there are 68.7% of IB1-IVA eventually developing to distant metastasis of all the recurrences [12], and nearly 30% of patients would die of the recurrence or distant metastasis [13], bringing a great challenge to clinicians. Therefore, more effective therapeutic schedule is highly anticipated for recurrent and metastatic cervical cancer.

During the past 15 years, intensity-modulated radiotherapy (IMRT) has been introduced and improved the ability to conform to target volumes and the reduction in dose delivered to organs at risk (OAR), lessening the acute and chronic toxicity induced by the radiation [14]. With the development of radiotherapy technology, there should be a move forward from the previously forbidden area such as the treatment of recurrent and metastatic cervical cancer. According to Singh et al. report, 7 asymptomatic patients with isolated para-aortic recurrence received the EBRT and achieved 100% 5-year survival [15]. Based on this, we attempt to explore the effects of radiotherapy on the distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) in metastatic cervical cancer, that was metastasized from IB1-IVA (initial stage at first treatment), and IVB initially had metastatic disease in these areas at diagnosis.

Materials and methods

Patient selection

A total of 73 patients with distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) were enrolled in the analysis. These patients were classified into IB1-IVA and IVB group based on their initial stage of first treatment. All patients received radiotherapy in the Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center (China) between 2016.07 and 2022.06. The inclusion criteria were listed as follows: (1) pathological diagnosis with cervical cancer; (2) pathological or imaging diagnosis with metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.); (3) compliance with routine surveillance. These enrolled patients with a cancer history, distant organ metastasis, and inguinal lymph node metastasis were also excluded from the study. Informed consent was obtained from all the patients. The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center, Shanghai, China.

Radiotherapy

Patients received intensity-modulated radiotherapy (IMRT) with CT planned. Target delineation was based on the Radiation Therapy Oncology Group Consensus Guideline 2008 [16]. All the plans were conducted with a megavoltage simulator with a photon energy of 6 MV. EBRT plan optimization was accepted when 95% of the PTV volume was covered by the prescribed dose. CR, PR, and ORR were evaluated. According to the evaluation criteria for solid tumor efficacy (RECIST Version 1.1), CR (complete response): all tumor lesions completely disappeared, lasting for 4 weeks; PR (Partial response): The lesion shrinks by more than 30% and lasts for 4 weeks; Objective response rate (ORR)=(CR+PR) cases/total cases x 100%.

Statistical analysis

The 95% confidence interval (CI) was calculated using the Clopper–Pearson method. The probabilities of the PFS and OS were estimated by Kaplan–Meier analysis, and the log-rank test was conducted to compare survival curves between the two groups. $p<0.05$ was considered statistically significant. All data were analyzed with the software GraphPad Prism 6.

Results

Patient clinicopathological characteristics

A total of 73 patients were enrolled in the analysis. The baseline characteristics of the patients are summarized in Table 1.1. The median age was 50.4 years old (range: 31 to 78 years). The histological subtypes were composed of 91.8% (67/73) squamous cell carcinoma, 2.7% (2/73) adenocarcinoma, and 5.5% (4/73) other types. ECOG PS was scored as 71 patients (97.3%) with 0, and 2 patients (2.7%) with 1. These metastatic cervical cancer patients were classified into IB1-IVA (49.3%, 36/73) and IVB (50.7%, 37/73) group based on their initial stage of first treatment. Thereinto, the IB1-IVA patients ultimately developed to the distant metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.), and the patients with stage IVB who initially had the disease in these areas at diagnosis. The location of metastatic lymph nodes is

Table 1.1 Baseline patient characteristics

Characteristic	N (%)
Age (years)	50.4 ± 9.1
Histology	
Squamous cell carcinoma	67 (91.8)
Adenocarcinoma	2 (2.7)
Other	4 (5.5)
ECOG	
0	71 (97.3)
1	2 (2.7)
FIGO Stage (2018)	
IB1-IVA	36 (49.3)
IVB	37 (50.7)
FIGO Stage (2018)	
I	
IB1	1
II	
IIA	2
IIB	2
III	
IIIA	0
IIIB	3
IIIC1	10
IIIC2	17
IV	
IVA	1
IVB	37
Chemotherapy	
Y	59 (80.8)
N	14 (19.2)
Sites of Metastatic lymph nodes	
Cervical	1
Clavicular	27
Mediastinal	6
Cervical + Clavicular	6
Clavicular + Mediastinal	13
Cervical + Clavicular + Mediastinal	2
Aboved + Other (Subaxillary/ Interpleural/ Retroperitoneal/)	18

Table 1.2

Location	Dose	N (%)
hilar lymph nodes	5000 cGy/25fx	1
Mediastinal	5500 cGy/25fx	3
Mediastinal	5750 cGy/25fx	1
Clavicular/ Mediastinal	5880 cGy/28fx	5
Cervical	6000 cGy/30fx	2
Cervical/ Clavicular	6160 cGy/28fx	60
Cervical	6440 cGy/28fx	1

listed in Table 1.1. More than 80% of patients (80.8%; 59/73) received the chemotherapy (Table 1.1). The majority of chemotherapy regimens were TC (Paclitaxel and Carboplatin) and IFO + ndp (Ifosfamide and Nedaplatin). The selection of these two chemotherapy regimens was decided by the physician.

All patients received the intensity-modulated radiotherapy (IMRT) with CT planned with radical radiation dose. The metastatic lymph nodes located in the

Table 1.3

Sites of Metastatic lymph nodes	CTV
Cervical	1
Clavicular	1 + 2
Mediastinal	3
Cervical + Clavicular	1 + 2
Clavicular + Mediastinal	1 + 2 + 3
Cervical + Clavicular + Mediastinal	1 + 2 + 3
Above + Other (Subaxillary/ Interpleural)	regional lymphatic drainage area involved by positive lymph nodes ± 1/2/3

1, Cervical IV regional lymphatic drainage area; 2, Clavicular regional lymphatic drainage area; 3, Mediastinal regional lymphatic drainage area involved by positive lymph nodes

cervical and clavicular were given the dose from 5880 to 6440 cGy. Among them, 82.2% (60/73) were given a dose of 6160 cGy/28fx. The mediastinal metastatic lymph nodes were given the dose from 5500 to 5880 cGy. The pulmonary hilum lymph nodes were given the dose of 5000 cGy due to their unique location. The location of metastatic lymph nodes and their corresponding radiation dose are listed in Table 1.2. The delineation of the gross tumor volume (GTV) was performed according to the pretherapeutic enhanced CT (Table 1.3). The clinical target volume (CTV) was performed in Table 1.3. CTV of cervical lymph nodes was cervical IV regional lymphatic drainage area. CTV of clavicular lymph nodes was cervical IV regional lymphatic drainage area and clavicular regional lymphatic drainage area. CTV of mediastinal lymph nodes was mediastinal regional lymphatic drainage area involved by positive lymph nodes. A 5–7 mm margin of CTV expansion was used as the planning target volume (PTV). A monthly follow-up was ensured for the first 6 months after the radiotherapy.

Survival and recurrence analysis

During the follow-up period, 73 patients were evaluated for treatment response. 9 (12.3%) patients achieved CR and 50 (68.5%) patients achieved PR. The ORR was 80.8% (95% CI: 69.9–89.1). Moreover, 7 (9.6%) patients were confirmed SD, and 7 (9.6%) patients were confirmed PD. The DCR was 90.4% (95% CI: 81.2–96.1; Table 2.1). Moreover, for all patients, the median PFS was 9 months (Fig. 1), and the median OS was 27 months (Fig. 2), which is 10 months longer than the reported OS of 17.0 months (27 months VS 17.0 months) receiving the combined treatment of bevacizumab and chemotherapy, without receiving the radiotherapy in the patients with recurrent, persistent, or metastatic cervical cancer [6]. Moreover, our OS is also 14 months longer than the reported OS of 13.0 months (27 months VS 13.0 months) just receiving the chemotherapy [6] in patients with recurrent, persistent, or metastatic cervical cancer. The results showed

Table 2.1 Overall tumor response in patients

Parameter	*N* (%)
Complete Response (CR)	9 (12.3)
Partial Response (PR)	50 (68.5)
Stable Disease (SD)	7 (9.6)
Progressive Disease (PD)	7 (9.6)
ORR (CR + PR), 95%CI	59 (80.8), 69.9–89.1
DCR (CR + PR + SD), 95%CI	66 (90.4), 81.2–96.1

Data are presented as N (%) unless otherwise specified. Responses were assessed in accordance with RECIST version 1.1. Only confirmed responses were included

ORR, overall response rate; DCR, disease control rate; CI, confidence interval

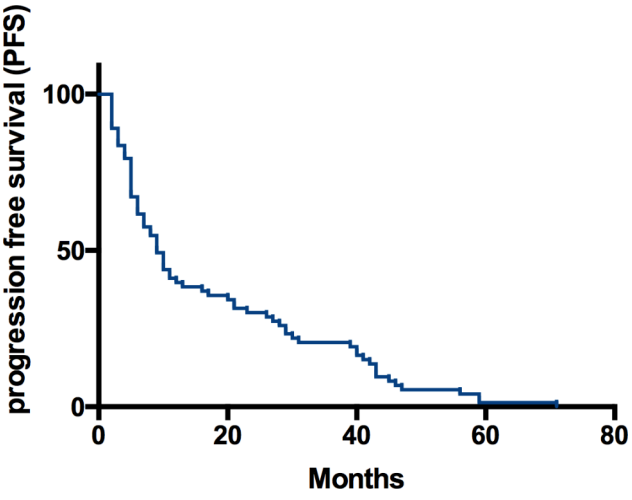

Fig. 1 Progression-free survival (PFS) for total patients

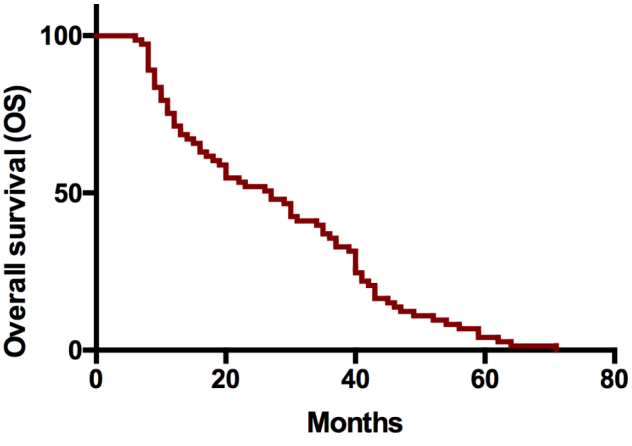

Fig. 2 Overall survival (OS) for total patients

that the radiotherapy had quite satisfactory local control rates, and could greatly prolong the OS of metastatic cervical cancer.

Subgroup survival analysis in stratified stage

49.3% (36/73) of patients were carefully examined to have no distant metastasis at the initial visit, and were identified as IB1-IVA. These patients ultimately developed

Table 2.2 Subgroup analysis for tumor response in patients with stage IB1-IVB

Stage	Parameter	*N* (%)
IB1-IVA	Complete Response (CR)	4 (11.1)
	Partial Response (PR)	28 (77.8)
	Stable Disease (SD)	1 (2.8)
	Progressive Disease (PD)	3 (8.3)
	ORR (CR + PR), 95%CI	32 (88.9), 73.9–96.9
	DCR (CR + PR + SD), 95%CI	33 (91.7), 77.5–98.2
IVB	Complete Response (CR)	5 (13.5)
	Partial Response (PR)	22 (59.5)
	Stable Disease (SD)	6 (16.2)
	Progressive Disease (PD)	4 (10.8)
	ORR (CR + PR), 95%CI	27 (73.0), 55.9–86.2
	DCR (CR + PR + SD), 95%CI	33 (89.2), 74.6–97.0

Data are presented as N (%) unless otherwise specified. Responses were assessed in accordance with RECIST version 1.1. Only confirmed responses were included

ORR, overall response rate; DCR, disease control rate; CI, confidence interval

to the distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.). 50.7% (37/73) patients were identified as IVB with the distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) at their initial visit. These IVB patients had no distant parenchymal organ metastasis such as lung, liver, bone, and peritoneum.

36 IB1-IVA patients were evaluated for treatment response. 4 (11.1%) patients achieved CR and 28 (77.8%) patients achieved PR. The ORR was 88.9% (95% CI: 73.9–96.9). Moreover, 1 (2.8%) patient was confirmed to have SD, and 3 (8.3%) patients were confirmed PD. The DCR was 91.7% (95% CI: 77.5–98.2; Table 2.2). 37 IVB patients were also evaluated for treatment response. 5 (13.5%) patients achieved CR and 22 (59.5%) patients achieved PR. The ORR was 73.0% (95% CI: 55.9–86.2). Moreover, 6 (16.2%) patients were confirmed to have SD and 4 (10.8%) patients were confirmed PD. The DCR was 89.2% (95% CI: 74.6–97.0; Table 2.2).

For IB1-IVA, the median PFS was 11 months (Fig. 3), and the median OS was 30.5 months (Fig. 4). Compared to a retrospective study about cervical cancer recurrence after concurrent chemoradiotherapy (CCRT), in which 57 patients were treated with only systemic chemotherapy, their median OS was 18 months and ORR was 15.7%. Obviously, the patients of recurrence and metastasis receiving the radiotherapy in our study could achieve better therapeutic effects and live at least 12.5 months longer than the chemotherapy group [7, 8]. Some studies found that the patients with recurrence after CCRT who were not candidates for surgical resection or salvage radiotherapy have a dismal prognosis with a reported 1-year survival rate between 15 and 20% [17]. Compared to these previously reported studies, our radiotherapy study significantly improved the patients' OS.

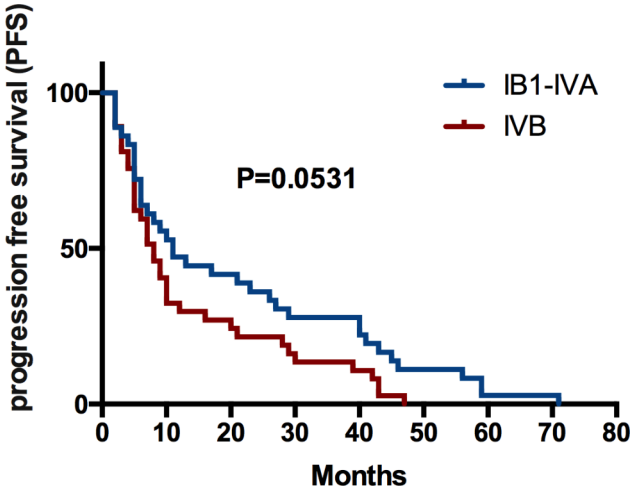

Fig. 3 Progression-free survival (PFS) of IB1-IVA group and IVB group

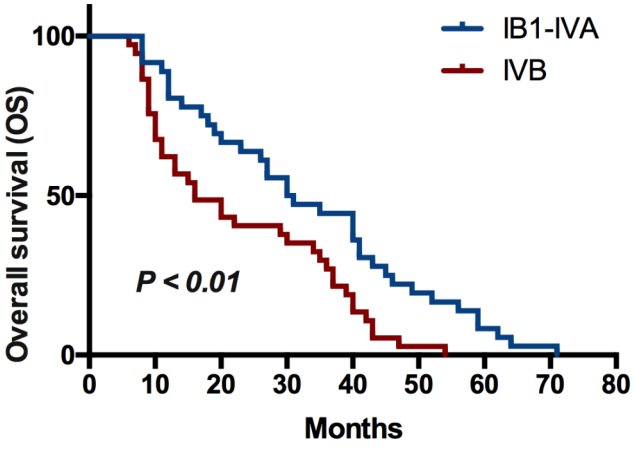

Fig. 4 Overall survival (OS) of IB1-IVA group and IVB group

The prognosis of radiotherapy in our study was also improved for IVB. The median PFS was 8 months (Fig. 3), and the median OS was 16 months (Fig. 4). Notably, although the OS of IB1-IVA is better than IVB ($P<0.01$, Fig. 4), there is no significant statistical difference between the two groups of PFS ($P=0.0531$, Fig. 3).

These results showed that radiotherapy for the distant metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) could effectively delay tumor growth and metastasis. IVB patients also could benefit from radiotherapy, indicating that the patients could have a better quality of life for a longer time. Actually, until now, the prognosis of patients with metastatic cervical cancer is poor with a median survival of 8–13 months despite of emerged chemotherapy and immunotherapy [18]. So, our study brings another option for metastatic cervical cancer and provides a significantly brand-new insight into the treatment.

Table 3 Adverse events

Adverse Events	Grade 1 + 2 (*N*)	Grade 3 + 4 (*N*)
Esophagitis	0	0
Nausea	0	0
Dysphagia	0	0
Chest wall pain	0	0
Bronchitis	0	0
Cough	0	0
Pneumonitis	0	0
Radiation-induced cardiac inflammation	0	0
Radiation myelitis	0	0
Leukocyte (×1000)	9	2
Platelet (×1000)	5	0
Hemoglobin(g)	2	1

Toxicity and safety analyses

Acute effects were not observed in the majority of patients such as radiation esophagitis, acute radiation lung disease, radiation-induced cardiac injury, and myelosuppression. The radiotherapy did not significantly increase the risk of myelosuppression. All adverse effects during the radiotherapy and follow-up were listed in Table 3.

Discussion

Cervical cancer (CC) is quite common in gynecologic cancer and can affect millions of lives globally, which is associated with HPV infection [19]. After initial treatment, the distant metastasis rate is respectively 16%, 31%, 26%, 39%, and 75% in stage IB, IIA, IIB, III, and IVA in cervical cancer [20]. Despite all these years of efforts, recurrent or metastatic cervical cancer always exhibits a very weak response to palliative chemotherapy and has a very poor prognosis. Actually, there are some studies on FIGO stage IIB-IVA reporting that 28% of patients suffered the distant relapse with 4.9% progression-free survival and 21.3% 5-year and overall survival (OS) [21]. The outcome of metastatic patients would vary depending on the location of tumor metastasis, but are generally worse than locoregional recurrence [7]. Actually, the patients have limited treatment options after recurrence or metastasis, especially the patients who are unresponsive to second-line or later treatment in cervical cancer [22]. It is urgent to explore novel therapeutic schedules for these patients with recurrent and metastatic cervical cancer.

In our study, 12.3% of patients achieved CR and 68.5% of patients achieved PR. The ORR was 80.8%. The DCR was 90.4%. Moreover, for these metastatic patients, the median PFS was 9 months, and the median OS was 27 months. Our results showed that the radiotherapy achieved satisfactory local control, and could

greatly prolong the OS of metastatic cervical cancer. For IB1-IVA, 11.1% of patients achieved CR and 77.8% of patients achieved PR. The ORR was 88.9%. The DCR was 91.7%. Their median PFS was 11 months, and the median OS was 30.5 months, which is much longer than the reported. For IVB, 13.5% of patients achieved CR and 59.5% of patients achieved PR. The ORR was 73.0%. The DCR was 89.2%. Their median PFS was 8 months, and the median OS was 16 months, which is also longer than the reported. Our results well demonstrated that the metastatic patients only with distant cervicothoracic metastatic lymph nodes (cervical/ clavicular/ mediastinal et al.) could benefit from the radiotherapy. To our knowledge, this is the first study to evaluate the efficacy and safety of radiotherapy in metastatic cervical cancer and reveal a survival benefit from the radiotherapy in these patients.

As a matter of fact, there have been great efforts to explore how to improve the prognosis of recurrent and metastatic cervical cancer. The phase III study of cisplatin monotherapy in stage IVB cervical cancer revealed that the median PFS was 2.8 months [23]. A phase II study of topotecan, which was applied as a single-agent second-line therapy in persistent or recurrent cervical cancer, illustrated that the median PFS was only 2.4 months [24]. Unfortunately, these results were not satisfactory. So, a large number of clinical studies turned to focus on anti-angiogenic therapy, which is confirmed to be an effective treatment for solid tumors. The GOG 240 trial found there existed the survival benefit of bevacizumab in combination with chemotherapy in recurrent or metastatic cervical cancer [25], as bevacizumab is also revealed to could bring significant improvements in activity, with its good tolerance in these patients with recurrent cervical cancer in the Gynecologic Oncology Group (GOG) 227 C trial [26]. However, compared to our radiotherapy for metastatic lymph nodes, combined treatment might lead to severe side effects and poor maintenance. Moreover, both the median OS (17 months) and the median PFS (8.2 months) are shorter than our results of radiotherapy. However, the patients on GOG 240 had more widespread metastatic disease compared to the patients in our study because that our study excluded the patients with distant parenchymal organ metastasis. The research by Colombo et al. also analyzed the patients with persistent, recurrent, or metastatic cervical cancer with a 1:1 ratio to receive pembrolizumab or placebo, and showed that progression-free and overall survival was longer with pembrolizumab than with placebo. At present, we preferred to radiotherapy for the cervicothoracic metastatic lymph nodes without distant parenchymal organs metastasis such as lung, liver, bone, and peritoneum, but we would choose to use pembrolizumab in more widespread metastatic disease in cervical cancer referencing the research by Colombo et al. [27]. There are other clinical trials currently underway to explore immunotherapy for recurrent or metastatic cervical cancer. Cadonilimab (AK104) is applied as monotherapy for recurrent patients after failed platinum-based chemotherapy, and acquired 33% ORR, and higher in PDL-1 positive patients [28]. Moreover, Antibody drug-conjugate (ADC) targeting tissue factor (TF) is also studied in the phase 2 trial Innova TV 204/GOG-3023/ENGOT-cx6, and showed good and durable antitumor activity, with 24% ORR and median duration response of 8.3 months [29].

In conclusion, as the first trial of radiotherapy in metastatic cervical cancer, we showed the application of radiotherapy for the cervicothoracic metastatic lymph nodes in metastatic patients and reported the survival benefit brought by the radiotherapy. As it is not a randomized trial, a prospective study with more widespread metastatic disease and longer follow-up are needed to confirm the clinical efficacy and safety of radiotherapy in the future.

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Author contributions
FC and XJ and SPL wrote the main manuscript text and FC and ZJ and SPL prepared figures and tables. KGH and WXH provided ideas and guidance. All authors reviewed the manuscript.

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No.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center, Shanghai, China. Informed consent was obtained from all the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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