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CLINICAL ARTICLE

Gynecology

The association between additional radiotherapy after systemic chemotherapy and the prognosis of stage FIGO 2018 IVB cervical cancer

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Abstract

Objective: Systemic platinum-based chemotherapy is the first-line treatment of choice for metastatic cervical cancer. While subsequent radiotherapy after primary chemotherapy is a potential option, its benefit remains unclear. This multicenter retrospective study aimed to evaluate whether post-chemotherapy radiotherapy improves the prognosis of metastatic cervical cancer.

Methods: We retrospectively analyzed 46 eligible patients, including 22 patients receiving chemotherapy-alone and 24 patients receiving chemotherapy followed by subsequent radiotherapy. Medical records were retrospectively reviewed for patient characteristics, subsequent treatment modality, adverse events during the treatment course, metastasis site, recurrence or progression, and recurrence sites. Fisher exact test or chi-squared test, the Mann–Whitney *U* test, log-rank test, and Cox proportional hazards model were used.

Results: The 2-year overall survival (OS) rate for all patients was 47%, with the median OS of 24.8 months. Patients receiving chemotherapy alone (chemotherapy-alone group) had a 2-year OS rate of 23%, while those receiving subsequent radiotherapy (chemotherapy-radiotherapy group) had a significantly higher OS rate of 67% (HR = 2.83, $P = 0.006$). The 2-year progression-free survival (PFS) rates were 9% and 33%, respectively (HR = 3.25, $P = 0.010$). Serious adverse events occurred in 46.2% of the chemotherapy-alone group and 29.2% of the chemotherapy-radiotherapy group during subsequent treatment ($P = 0.249$).

Conclusion: Post-chemotherapy radiotherapy may improve the prognosis of metastatic cervical cancer without increasing serious adverse events. Further prospective studies are warranted to validate these findings.

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KEYWORDS
advanced cancer, cervical cancer, chemotherapy, metastasis, prognosis, radiotherapy

1 | INTRODUCTION

The prognosis for stage IVB cervical cancer has remained poor irrespective of multimodal cancer treatment. The 5-year survival rate for IVB cervical cancer is 32% in Japan,[1] whereas that in the USA is 19.4%.[2] Notably, these survival data were based on the staging following the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system. FIGO 2018 classified the patients with para-aortic lymph node metastases alone as stage IVB as were the patients with distant metastases. Conversely, FIGO 2018 stage IVB includes only distant metastasis and not para-aortic lymph node metastasis alone. Therefore, the current survival outcome of patients with FIGO 2018 stage IVB may have a worse prognosis than the FIGO 2009 survival outcome because para-aortic lymph node metastasis alone was better than distant organ metastasis.[3]

First-line treatment for metastatic cervical cancer is systemic chemotherapy, which may be followed by additional personalized local treatment depending on the site of the disease. Recently, immune checkpoint inhibitors (ICIs) have been used to treat various cancer types, and the combination of paclitaxel (PTX), cisplatin or carboplatin (CBDCA), bevacizumab (Bev), and pembrolizumab has become the preferred first-line regimen for persistent, recurrent, and metastatic cervical cancer.[4] The role of radiotherapy as a local control treatment is being investigated in metastatic cervical cancer. Radiotherapy has been effectively applied in cervical cancer with oligometastasis. Definitive pelvic radiotherapy, as part of treatment in patients with stage IVB cervical cancer, may improve oncologic outcomes compared with systemic chemotherapy with or without palliative radiotherapy.[5] Ultimately, treatment decisions—whether curative or palliative—are made on an individual basis by the physician following systemic chemotherapy.[6]

We conducted a multicenter collaborative retrospective study to evaluate the association between subsequent radiotherapy and prognosis in patients with FIGO 2018 stage IVB cervical cancer, as well as to assess treatment-related adverse events.

2 | MATERIALS AND METHODS

2.1 | Patients

This was a retrospective cohort study which included patients diagnosed with stage IVB cervical cancer according to FIGO 2018, who had been treated with chemotherapy as primary treatment from January 2011 to December 2021 at the Department of Obstetrics and Gynecology of Osaka University Hospital, Osaka General Medical Center, Kansai Rosai Hospital, Kaizuka City Hospital, Nishinomiya Prefectural Hospital, and Toyonaka City Hospital, Japan.

We retrospectively reviewed the medical records for the age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), gravida, parity, Union for International Cancer Control (UICC) tumor, node, and metastasis (TNM) classification, the largest tumor diameter in the whole body, tumor histology, the subsequent treatment modality, adverse events during each treatment course, metastasis site, recurrence or progression, and recurrence site. We excluded cases with ovarian metastases or without the details of treatment and the prognosis.

The adverse effects (AE) during chemotherapy and radiation therapy were assessed based on Common Terminology Criteria for Adverse Events.[7] The response to chemotherapy was evaluated using computed tomography. Complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) were defined following the Response Evaluation Criteria in Solid Tumors (RECIST).[8] The primary chemotherapy regimens used as first-line treatment were platinum-based. Following primary chemotherapy, the subsequent treatment was determined by physician preference. At Osaka University Hospital, radiotherapy was indicated for localized uterine disease.[9] In other hospitals, treatment decisions were made according to the preference of individual physicians.

We obtained the prognosis and survival outcome, as of December 1, 2023. The overall survival (OS) and progression-free survival (PFS) were calculated from primary treatment initiation to the final follow-up period and first relapse or progression, respectively.

2.2 | Statistical analysis

MedCalc (MedCalc Software, Ostend, Belgium) was used for statistical analysis. A Fisher exact test or chi-squared test was utilized to analyze differences between the two groups for categorical variables. The Mann–Whitney *U* test was used for the evaluation between the group for continuous and non-continuous variables. OS and PFS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance with the log-rank test and Cox proportional hazards model. A *P* value of less than 0.05 indicated statistical significance.

2.3 | Compliance with ethical standards

The Institutional Review Board and the Ethics Committee of the Osaka University Hospital approved this study (no. 22393[T9]-3). Informed consent was obtained as an opt-out on the website of each

institution. This study was conducted under all relevant guidelines and regulations.

3 | RESULTS

There were 50 patients with FIGO 2018 stage IVB cervical cancer receiving chemotherapy for the first treatment. Two patients lacking the details of treatment and prognosis, and two patients with ovarian metastasis were excluded. This study finally included 46 eligible patients. The median follow-up time was 22 months (range: 1–128). Table 1 shows the patient characteristics. The median age was 58 (range: 31–89), and the median BMI was 21.6 (16.1–40.0). The age, BMI, gravida, and parity were similar in the subsequent chemotherapy and radiotherapy groups.

T category following the UICC TNM classification was 1b, 2a, 2b, 3a, 3b, and 4 in five (10.9%), one (2.2%), 18 (39.1%), two (4.3%), 11 (23.9%), and nine (19.6%) patients, respectively. Regional lymph node metastases were present in 42 (91.3%) patients. The sites of distant metastasis varied. Non-regional lymph node, bone, ovarian, peritoneal, and distal organ metastases were present in 20 (43.5%), nine (19.6%), four (8.7%), nine (19.6%), and 18 (39.1%) patients, respectively. Overall, the TNM classification of the tumors and the metastatic sites were statistically comparable in both groups (Table 1). Pathologic microscopic assessment of cervical biopsy tissue revealed that 30 (65.2%), nine (19.6%), and seven (15.2%) patients were diagnosed as squamous cell carcinoma, adenocarcinoma, and other carcinoma types, respectively. The median largest tumor diameter of the tumor was 55 mm (17–102).

Most patients, 45 (97.8%), received paclitaxel (PTX) of 175 mg/m^2, carboplatin (CBDCA) AUC 5, and with or without bevacizumab (Bev) of 15 mg/kg, triweekly, 3–6 times, as primary treatment. The remaining one patient (2.2%) received irinotecan (CPT-11) of 60 mg/m^2 and cisplatin (CDDP) of 60 mg/m^2, every 4 weeks, for six times (Table 2). Primary systemic chemotherapy resulted in four (8.7%) CR, 16 (34.8%) PR, seven (15.2%) SD, and

TABLE 1 Patient characteristics.

	All ($n=46$)	Ch alone ($n=22$)	Ch + RT ($n=24$)	*P* value
Age (years old)	58 (31–89)	60 (31–89)	57 (38–79)	0.397
BMI (kg/m^2)	21.6 (16.1–40.0)	21.6 (16.4–29.2)	22.0 (16.1–40.0)	0.775
G	2 (0–8)	2 (0–8)	2 (0–6)	0.786
P	2 (0–6)	2 (0–6)	2 (0–3)	0.891
The UICC TNM classification				
T				
1b	5 (10.9)	2 (9.1)	3 (12.5)	0.519
2a	1 (2.2)	1 (4.5)	0	
2b	18 (39.1)	9 (40.9)	9 (37.5)	
3a	2 (4.3)	2 (9.1)	0	
3b	11 (23.9)	5 (22.7)	6 (25.0)	
4	9 (19.6)	3 (13.6)	6 (25.0)	
N				
Positive	42 (91.3)	19 (86.4)	23 (95.8)	0.336
M				
Non-regional lymph nodes	20 (43.5)	8 (36.4)	12 (50.0)	0.323
Bone	9 (19.6)	4 (18.2)	5 (20.8)	
Ovary	4 (8.7)	3 (13.6)	1 (4.2)	
Peritoneum	9 (19.6)	7 (31.8)	2 (8.3)	
Distal organs	18 (39.1)	10 (45.5)	8 (33.3)	
Histology				
SCC	30 (65.2)	12 (54.5)	18 (75.0)	0.323
Adenocarcinoma	9 (19.6)	6 (27.3)	3 (12.5)	
Other types	7 (15.2)	4 (18.2)	3 (12.5)	
Largest tumor diameter (mm)	55 (17–102)	47 (17–92)	60 (27–102)	0.675

Note: BMI, calculated as weight in kilograms divided by the square of height in meters. Data are shown as median (range) or *n* (%).

Abbreviations: BMI, body mass index; Ch, chemotherapy; G, gravida; P, parity; RT, radiotherapy; SCC, squamous cell carcinoma; TNM, tumor, node and metastasis; UICC, Union for International Cancer Control.

TABLE 2 Characteristics of primary chemotherapy.

	All ($n=46$)	Ch alone ($n=22$)	Ch + RT ($n=24$)
Regimens			
TC ± Bev	45 (97.8)	22 (100)	23 (95.8)
CPT-11 + CDDP	1 (2.2)	0	1 (4.2)
Adverse events ≥ Grade 3	6 (13.0)	5 (22.7)	1 (4.1)
Neutropenia	0	0	0
Anemia	1 (2.2)	1 (4.5)	0
Thrombocytopenia	1 (2.2)	0	1 (4.1)
Febrile neutropenia	1 (2.2)	0	1 (4.1)
Elevated ALT	1 (2.2)	1 (4.5)	0
General fatigue	3 (6.5)	3 (13.6)	0
Numbness	1 (2.2)	1 (4.5)	0
Response			
CR	4 (8.7)	2 (9.1)	2 (8.3)
PR	16 (34.8)	5 (22.7)	11 (45.8)
SD	7 (15.2)	3 (13.6)	4 (16.7)
PD	19 (41.3)	12 (54.6)	7 (29.2)

Note: Data are shown as *n* (%).

Abbreviations: ALT, alanine aminotransferase; Bev, bevacizumab; CDDP, cisplatin; Ch, chemotherapy; CPT-11, irinotecan; CR, complete response; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease; TC, paclitaxel and carboplatin.

TABLE 3 Characteristics of subsequent treatment.

	Ch alone	Ch + RT
Discontinuation of treatment	9 (40.9) (CR1, PR2, SD1, PD5)	0
Subsequent chemotherapy	13	0
Regimens		
Bev	5 (38.5)	
CPT11 (+NDP or 5FU)	7 (53.8)	
Etoposide	1 (7.7)	
Adverse events ≥ Grade 3	6 (46.2)	
Neutropenia	3 (23.1)	
Anemia	2 (15.4)	
General fatigue	2 (15.4)	
Hypertension	1 (7.7)	
Gastric ulcer	1 (7.7)	
Subsequent radiotherapy	0	24
Treatment type		
Combination of EBRT and ICBT		8 (33.3%)
EBRT alone		15 (62.5%)
ICBT alone		1 (4.2%)
Adverse events ≥ Grade 3		7 (29.2%)
Neutropenia		5 (20.8%)
Thrombopenia		3 (12.5%)
Anemia		2 (8.3%)

Note: Data are shown as *n* (%).

Abbreviations: 5FU, fluorouracil; Bev, bevacizumab; Ch, chemotherapy; CPT-11, irinotecan; CR, complete response; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; NDP, nedaplatin; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

19 (41.3%) PD. Overall, six (13.0%) patients experienced grade ≥3 adverse events, including one anemia (2.2%), one thrombocytopenia (2.2%), one febrile neutropenia (2.2%), one elevated aspartate aminotransferase (ALT) (2.2%), three general fatigue (6.5%), and one numbness (2.2%).

After primary chemotherapy, nine (40.9%) patients discontinued chemotherapy due to their AEs or their own preference. The remaining 13 (59.1%) patients, including one CR (7.7%), three PR (23.1%), two SD (15.4%), and seven PD (53.8%) after primary chemotherapy, further received second-line regimens (chemotherapy-alone group) (Table 3). Conversely, 24 patients, including two (8.3%) CR, 11 (45.8%) PR, four (16.7%) SD, and seven (29.2%) PD after primary chemotherapy, switched to subsequent radiotherapy (chemotherapy-radiotherapy group) (Table 2). A higher PR was observed in the chemotherapy-radiotherapy group and a higher PD in the chemotherapy-alone group; however, the differences were not statistically significant. Eight (33.3%) patients received external beam radiation therapy (EBRT) for the whole pelvis with intracavity brachytherapy (ICBT), 15 (62.5%) received EBRT alone, and one (4.2%) received ICBT alone (Table 3).

During the subsequent treatment course, six (46.2%) patients experienced grade ≥3 adverse events (AEs) in the chemotherapy-alone group, including three neutropenia (23.1%), two anemia (15.4%), two general fatigue (15.4%), one hypertension (7.7%), and one gastric ulcer (7.7%). In the chemotherapy-radiotherapy group, seven (29.2%) patients experienced grade ≥3 AEs, including five neutropenia (20.8%), three thrombopenia (12.5%), and two neutropenia (8.3%). Both groups experienced no grade 5 AEs. Subsequent radiotherapy did not significantly increase AEs compared to subsequent chemotherapy ($P=0.249$).

The 2-year OS rate for all patients with stage IVB cervical cancer was 47% and the median OS was 24.8 months (Figure 1a). Subgroup analysis revealed that the 2-year OS rates were 24% and 61% in the chemotherapy-alone and chemotherapy–radiotherapy groups, respectively ($P=0.014$). The median OS was 17.8 months and 31.8 months, in each group, respectively. Patients treated with chemotherapy and subsequent radiotherapy demonstrated significantly better prognoses than those treated with chemotherapy alone (Figure 1b).

To evaluate the impact of subsequent treatment, we excluded nine patients who discontinued treatment after primary chemotherapy and analyzed only those who received further treatment.

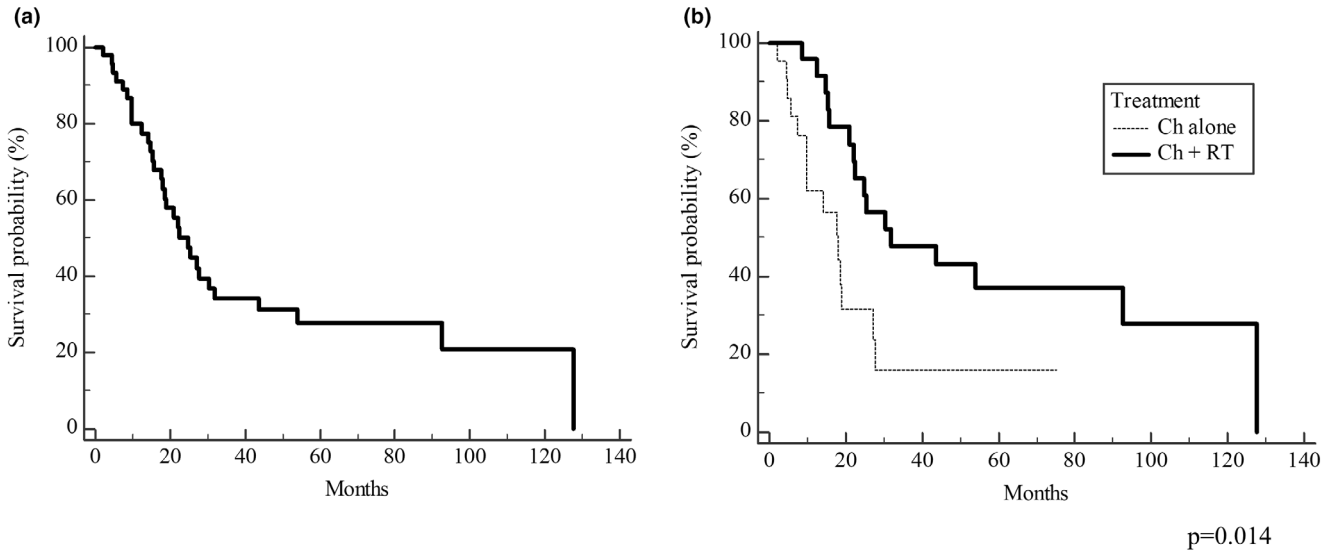

FIGURE 1 Kaplan–Meier curves of overall survival for stage IVB cervical cancer. (a) Overall survival rate for all patients with stage IVB cervical cancer. (b) Overall survival rate for the chemotherapy-alone and chemotherapy radiotherapy groups.

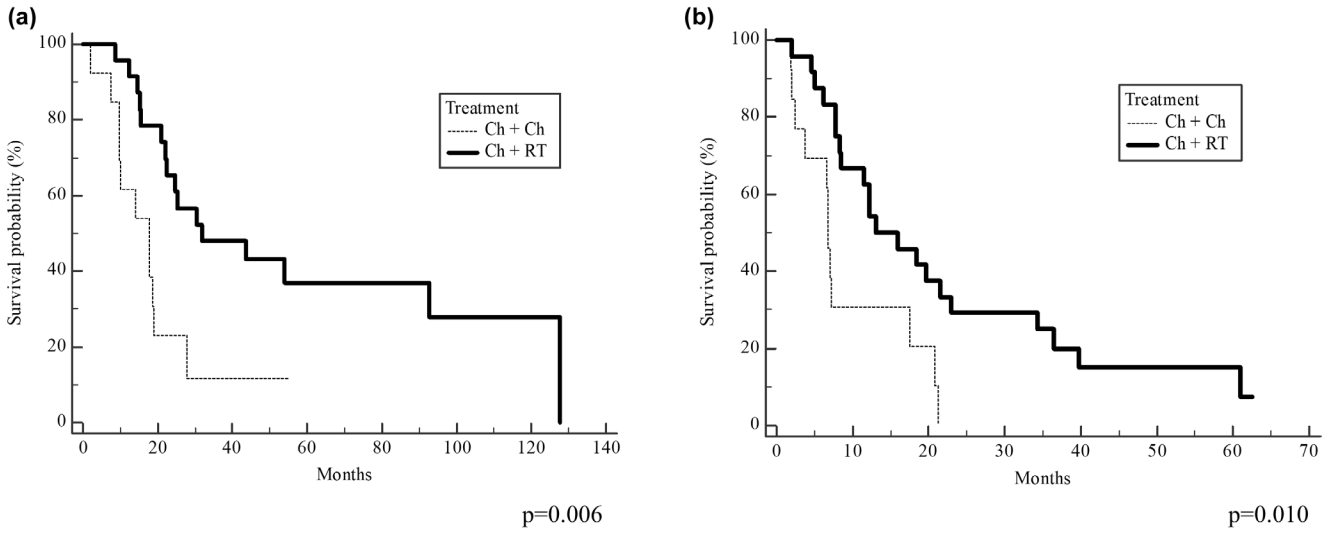

FIGURE 2 Kaplan–Meier curves of overall survival and progression-free survival for stage IVB cervical cancer treated with the subsequent chemotherapy and radiotherapy. (a) Overall survival rates for the subsequent chemotherapy and radiotherapy groups. (b) Progression-free survival rates for the subsequent chemotherapy and radiotherapy groups.

Two-year OS rates were 23% and 67% (HR = 2.83, $P = 0.006$) (Figure 2a), and 2-year PFS rates were 9% and 33% (HR = 3.25, $P = 0.010$) in the chemotherapy-alone and chemotherapy–radiotherapy groups, respectively (Figure 2b). Subsequent radiotherapy showed significantly longer OS and PFS for patients with stage IVB cervical cancer, compared to subsequent chemotherapy. Recurrence or progression in the pelvis and nonpelvis was reported in five (22.7%) and eight (33.3%) and in 14 (63.6%) and 13 (54.2%) patients of the chemotherapy-alone and chemotherapy–radiotherapy groups, respectively (Table 4). The local control effect of radiotherapy was equivalent to that of chemotherapy-alone but may have contributed to the longer survival of the chemotherapy–radiotherapy group.

4 | DISCUSSION

The present study revealed that chemotherapy and subsequent radiotherapy for patients with stage IVB cervical cancer contribute to a better prognosis than subsequent chemotherapy. Subsequent radiotherapy may explain the relatively favorable survival outcome of patients with stage IVB at 2.0 years of median OS.

The prognosis for metastatic cervical cancer remains poor irrespective of current chemotherapy regimens. In a previous study, the 5-year survival rate for patients with stage IVB cervical cancer was 29% in Japan[1] and the 5-year relative survival was <20% in the USA. Therapeutic options for metastatic cervical cancer remain limited, in reality.[10] In previous studies, the treatment response rate was

TABLE 4 Recurrence sites.

	Ch alone ($n=22$)	Ch + RT ($n=24$)
Pelvis	5 (22.7)	8 (33.3)
Uterus	5 (22.7)	5 (20.8)
Ovary	0	1 (4.2)
Pelvic bone	2 (9.1)	1 (4.2)
Lymph node	0	3 (12.5)
Non-pelvis	14 (63.6)	13 (54.2)
Lung	3 (13.6)	6 (25.0)
Liver	4 (18.2)	1 (4.2)
Bone	1 (4.5)	2 (8.3)
Peritoneum	5 (22.7)	3 (12.5)
Lymph node	3 (13.6)	6 (25.0)
Brain	0	1 (4.2)

Note: Data are shown as *n* (%).

Abbreviations: Ch, chemotherapy; RT, radiotherapy.

approximately 20%, the median PFS was <5 months, and overall survival was <10 months even with various chemotherapy regimens containing platinum agents.[11,12] Notably, the current survival outcome of patients with FIGO 2018 stage IVB cervical cancer may be worse than in the FIGO 2009 era, although they may be improving with the newly established treatment strategies. This is because para-aortic lymph node metastasis alone, included in FIGO 2009 stage IVB but not in FIGO 2018 stage IVB, exhibited a better prognosis than distant organ metastases. A previous study stated that the median OS of patients with stage IVB cervical cancer excluding those with para-aortic lymph node metastasis alone was 9 months.[3] Therefore, our survival outcomes of FIGO 2019 stage IVB appeared better than previous reports.

The KEYNOTE-826 trial demonstrated significant survival benefits of adding pembrolizumab (PEM) to the conventional platinum and taxane chemotherapy with or without bevacizumab, as a first-line systemic treatment for persistent, recurrent, or metastatic cervical cancer for PD-L1-positive patients, with at least PD-L1 combined score of 1 or more.[4] Now, patients with stage IVB cervical cancer may be treated with this combination therapy; however, they might not benefit from the additional effect of pembrolizumab. The subgroup analysis of 190 patients with distant metastasis in KEYNOTE-826 revealed that this regimen did not significantly improve their PFS (hazard ratio [HR]: 0.92, 95% confidence interval [CI]: 0.64–1.30) and OS (HR: 0.84, 95% CI: 0.56–1.26), either.[4]

Favorable outcomes have been recently reported with radiotherapy for primary or recurrent cervical cancer with oligometastases. Park et al. investigated local control and patient survival for recurrent or oligometastatic cervical cancer treated with stereotactic body radiotherapy using CyberKnife. The 2-year local PFS and OS rates were 82.5% and 57.5% and the 5-year local PFS and OS rates were 78.8% and 32.9%, respectively.[13] Ning et al. reported the effect of definitive radiotherapy in oligometastatic cervical cancer with metastatic disease involving ≤2 extra-pelvic/para-aortic sites, including supraclavicular (SCV) lymph nodes, mediastinal lymph nodes, or lung. The median OS was 50.7 months after completing radiotherapy, with 2-year and 3-year OS rates of 74% and 65%, respectively. Median PFS was 21.7 months, with 1- and 2-year PFS rates of 63% and 48%, respectively.[14] These reports indicate the existence of a subset of cases, even in stage IVB, where long-term survival is expected if radiotherapy is applied not only to the primary lesion and regional lymph nodes but also to distant metastases.

Recent retrospective studies have indicated that adding pelvic radiation to initial treatment for patients with FIGO 2009 stage IVA and IVB cervical cancer prolongs survival.[15,16] The largest study analyzed 2361 FIGO 2009 stage IVB cases with pelvic irradiation added to systemic chemotherapy and 808 cases with systemic chemotherapy-alone and revealed that radiation significantly prolonged median OS, with 14.4 months compared to 10.1 months in the systemic chemotherapy-alone group ($P<0.001$).[15] Another study that analyzed FIGO 2009 stage IVB 126 cases revealed that the addition of the pelvic radiation group exhibited a median OS of 41.6 months, compared to 17.6 months in the systemic chemotherapy-alone group, indicating a significant prolongation of 24 months ($P=0.006$).[16] These reports indicate that pelvic lesion control may reduce the progression of pelvic symptoms and prolong survival even in stage IVB. These findings support our results.

Definitive radiotherapy is another strategy as primary treatment for patients with stage IVB cervical cancer.[5,17] The definitive chemoradiation has been associated with better oncologic outcomes, including PFS, cause-specific survival, and OS.[5] Concurrent chemoradiotherapy (CCRT), including the whole pelvis, para-aortic, and left supraclavicular lymph node irradiation with platinum as a sensitizer, was performed in 25 patients with pelvic, para-aortic, and left supraclavicular lymph node metastases. CRs were achieved in 13 (52%) patients, with a median OS of 32 months and a 3-year survival rate of 49%.[17] This strategy should be confirmed in a prospective trial model in the future.

Recently, the combination of ICIs and radiotherapy (iRT) has demonstrated a potential. Historically, the abscopal effect referred to the phenomenon in which radiotherapy exerted the effects on non-irradiated tumors, suggesting that radiotherapy could stimulate the immune system. Nowadays, radiotherapy is widely accepted to provoke a systemic immune response, by inducing immunogenic cell death and neoantigen release. IRT is considered an ideal combination in terms of its synergistic effect and overcoming resistance mechanism.[18,19] The clinical efficacy of iRT has been demonstrated in non-small cell lung cancer (NSCLC), melanoma and some solid tumors.[20–22] More recently, evidence has emerged regarding its potential for treating locally advanced cervical cancer. The CALLA study, however, failed to show a survival benefit from adding durvalumab to CCRT.[23] In contrast, ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial reported that pembrolizumab plus CCRT improved the 2-year PFS rate to 68% compared with 57% in the placebo–CCRT group (HR: 0.70; 95% CI: 0.55–0.89; $P=0.0020$).[24] Despite these promising results regarding the synergistic effect of ICIs and radiotherapy, both studies excluded FIGO 2018 stage IVB cases, focusing solely

on locally advanced disease. Conversely, there are reports indicating the effectiveness of combining radiotherapy and ICIs for the treatment of metastatic lung cancer.[25] Future research should investigate the potential of iRT in the treatment of metastatic cervical cancer.

This study had several limitations. First, the small sample size reduced the statistical power, making it impossible to perform multivariate and propensity score-matching analyses to control for confounding factors and assess internal validity. Second, as a retrospective study, it was subject to inherent biases, including selection bias and differences in diagnostic criteria among hospitals. Additionally, the absence of a standardized treatment protocol, particularly regarding subsequent treatment after primary chemotherapy, may have introduced variability by physician's choice that influenced the results.

While prospective studies would be ideal, the rarity and heterogeneity of metastatic cervical cancer presents challenges to conducting such research. Considering that the study was conducted in multiple centers, with non-arbitrary treatment allocation, although non-random, radiotherapy after primary chemotherapy may be effective for patients with metastatic cervical cancer. Future larger-scale studies are warranted to confirm the potential survival benefits of subsequent radiotherapy in patients with metastatic cervical cancer.

5 | CONCLUSION

Adding radiotherapy to primary systemic chemotherapy was performed safely and may be associated with improved prognosis in metastatic cervical cancer. Further evaluation is necessary to establish its role as a treatment option for metastatic cervical cancer.

AUTHOR CONTRIBUTIONS

AM: Data curation, formal analysis, investigation, methodology and writing-original draft. MK: Conceptualization, data curation, investigation, methodology, writing-review and editing, and supervision. FI, TI, MT, YN, TY, EY, KI, EY, KM, TT: Resources. TK: Supervision.

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CONFLICT OF INTEREST STATEMENT

MK received honoraria from MSD Pharmaceuticals. The other authors declare no conflict of interest in the present study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Kiyoshi Y, Kurita T, Takahashi F, et al. Annual report of the Committee on Gynecologic Oncology, the Japan Society of Obstetrics and Gynecology: Annual Patient Report for 2020 and Annual Treatment Report for 2015. *J Obstet Gynaecol Res*. 2023;49:2584-2592.
2. https://seer.cancer.gov/statfacts/html/cervix.html. Accessed November 6, 2024.
3. Nishio S, Matsuo K, Yonemoto K, et al. Race and nodal disease status are prognostic factors in patients with stage IVB cervical cancer. *Oncotarget*. 2018;9(64):32321-32330. doi:10.18632/oncotarget.25962
4. Monk BJ, Colombo N, Tewari KS, et al. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. *J Clin Oncol*. 2023;41:5505-5511.
5. Viveros-Carreño D, Vieira-Serna S, Grillo-Ardila CF, et al. Definitive pelvic radiotherapy for patients with newly diagnosed stage IVB cervical cancer: a systematic review. *Int J Gynecol Cancer*. 2023;33(7):1057-1062. doi:10.1136/ijgc-2023-004465
6. https://www.jsgo.or.jp/guideline/js/pdfjs/web/viewer.html?file=/guideline/img/keiganguide2022-03.pdf
7. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50
8. https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fctep.cancer.gov%2Fprotocoldevelopment%2Fdocs%2Fquickrcst.doc&wdOrigin=BROWSELINK
9. Fujiwara M, Isohashi F, Mabuchi S, et al. Efficacy and safety of nedaplatin-based concurrent chemoradiotherapy for FIGO stage IB2–IVA cervical cancer and its clinical prognostic factors. *J Radiat Res*. 2014;56:305-314.
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2019;69:7-34.
11. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2009;27(28):4649-4655. doi:10.1200/JCO.2009.21.8909
12. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2004;22(15):3113-3119. doi:10.1200/JCO.2004.04.170
13. Park HJ, Chang AR, Seo Y, et al. Stereotactic body radiotherapy for recurrent or oligometastatic uterine cervix cancer: a cooperative study of the Korean Radiation Oncology Group (KROG 14-11). *Anticancer Res*. 2015;35:5103-5110.
14. Ning MS, Ahobila V, Jhingran A, et al. Outcomes and patterns of relapse after definitive radiation therapy for oligometastatic cervical cancer. *Gynecol Oncol*. 2018;148:132-138.
15. Wang Y, Farmer M, Izaguirre EW, et al. Association of definitive pelvic radiation therapy with survival among patients with newly diagnosed metastatic cervical cancer. *JAMA Oncol*. 2018;4:1288-1291.
16. Perkins V, Moore K, Vesely S, et al. Incorporation of whole pelvic radiation into treatment of stage IVB cervical cancer: a novel treatment strategy. *Gynecol Oncol*. 2020;156:100-106.
17. Kim JY, Kim JY, Kim JH, Yoon MS, Kim J, Kim YS. Curative chemoradiotherapy in patients with stage IVB cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. *Int J Radiat Oncol Biol Phys*. 2012;84:741-747.
18. Galluzzi L, Aryankalayil MJ, Coleman CN, Formenti SC. Emerging evidence for adapting radiotherapy to immunotherapy. *Nat Rev Clin Oncol*. 2023;20:543-557.
19. Zhang Z, Liu X, Chen D, Yu J. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. *Signal Transduct Target Ther*. 2022;7:258.
20. Chen D, Menon H, Verma V, et al. Response and outcomes after anti-CTLA4 versus anti-PD1 combined with stereotactic body radiation therapy for metastatic non-small cell lung cancer: retrospective analysis of two single-institution prospective trials. *J Immunother Cancer*. 2020;8:e000492.

21. Hiniker SM, Reddy SA, Maecker HT, et al. A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. *Int J Radiat Oncol Biol Phys*. 2016;96:578-588.
22. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol*. 2018;36:1611-1618.
23. Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2023;24:1334-1348.
24. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet*. 2024;403:1341-1350.
25. Theelen WSME, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Respir Med*. 2021;9:467-475.

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