ELSEVIER
Brachytherapy xxx (xxxx) xxx
BRACHYTHERAPY

Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump

Xiao-Li Yu[1,2,#], Jiang Hu[3,#], Xin-Ling Cai[4], Jian-Nan Fang[1,2], Jin Yang[1,2], Ming Luo[1,2], Shou-Min Bai[1,2,*]

[1] *Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

[2] *Department of Radiation Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

[3] *Department of Radiation Oncology, Sun Yat-Sen University Cancer Center and State Key Laboratory of Oncology in Southern China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

[4] *Department of Radiation Oncology, Shenshan Medical Center, Memorial Hospital of Sun Yat-sen University, Shanwei, China*

ABSTRACT

OBJECTIVE: This study aimed to determine the effectiveness of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, and to identify the candidates most likely to benefit.

METHODS: Newly diagnosed, non-metastatic cervical cancer patients treated in our hospital between January 2012 and November 2015 were retrospectively reviewed. Early stage patients receiving radical surgery and needing adjuvant external radiotherapy were included, but those with positive stump were excluded. All patients received external radiotherapy. They were divided into two groups: one group received vaginal brachytherapy and the other did not. The 5-year local-regional recurrence free survival (LRRFS) and overall survival (OS) rates in the two groups were compared.

RESULTS: Two hundred and twenty-five patients were included in this study; while 99 received brachytherapy, 126 did not. The brachytherapy group had significantly superior 5-year LRRFS (87.7% vs. 72.5%, $p = 0.004$), but did not show a significant overall survival benefit (78.4% vs. 75.3%, $p = 0.055$). In multivariate analysis, brachytherapy, pathological type, high-risk factors, duration of radiotherapy, and transfusion were independent prognostic factors for 5-year LRRFS. In stratified analysis, the brachytherapy group showed superior LRRFS in those meeting Sedlis criteria ($p = 0.017$).

CONCLUSION: The combination of external beam radiation therapy and brachytherapy can improve LRRFS in post-operative cervical cancer patients with risk factors other than positive stump. Therefore, brachytherapy should be considered for these patients.

Keywords: Brachytherapy; Cervical cancer; Post-operative; External radiation therapy; Risk factor

Introduction

Cervical cancer is the fourth most common cancer and the sixth leading cause of cancer death in women, with about 85% of all cases being reported from developing countries (1,2). Early stage cervical cancer can be cured by surgery; additional adjuvant radiotherapy is recommended for patients with high-risk factors (HRF) such as positive/close vaginal stump, positive lymph node, or parametrial invasion or intermediate-risk factors (IRF) such as interstitial infiltration, tumor size, and lymphovascular space invasion meeting Sedlis criteria (3). Although adjuvant

Received 1 June 2022; received in revised form 15 September 2022; accepted 7 October 2022; Available online xxx

Disclosures: The authors indicated no financial disclosures or potential conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author. Shou-Min Bai, Department of Radiation Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 33 Ying feng Road, Guangzhou 510120, China, Tel.: +86-20-34070680; fax: +86-20-34070680.

E-mail address: baishm@mail.sysu.edu.cn (S.-M. Bai).

# Contributed equally to this study.

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

therapy can improve long-term survival (4,5), recurrence is reported in 8%–30% of patients (6–9). In patients with recurrence, treatment options are limited and usually associated with high risk of complications (10). Therefore, adequate adjuvant therapy is crucial in patients with adverse prognostic factors.

Brachytherapy (BT), with its advantages of high dose to the tumor and steep attenuation, is irreplaceable as boost for external beam radiation therapy (EBRT) in the treatment of locally advanced cervical cancer (11). However, for post-operative patients, the role of BT remains unclear. Li et al. convincingly demonstrated that the addition of BT to EBRT improves survival in patients with positive margins after hysterectomy (12). Kim et al. and Fajardo et al. found that adjuvant concurrent chemoradiotherapy after hysterectomy improves survival of patients with squamous cell carcinoma, but not of those with adenocarcinoma; however, the addition of BT could eliminate the survival difference between the two pathological types (9,13). Wang et al. applied BT in their patients with IRF (14). The current National Comprehensive Cancer Network (NCCN) guidelines recommend EBRT "with or without" vaginal BT for patients with HRF (3). It is not clear whether patients with other adverse prognostic factors benefit from the addition of BT.

The aim of this study was to assess the efficacy of post-operative BT in cervical cancer patients with HRF or IRF and to identify the characteristics of candidates likely to benefit from the addition of BT.

Methods

Ethics Approval and Consent to Participate

This retrospective study was approved by the Ethics Committees of Sun Yat-sen Memorial Hospital, Sun Yat-sen University, and the requirement to obtain informed consent was waived [SYSEC-KY-KS-2020-027]. All the data were analyzed anonymously.

Patients

The clinical records of all newly diagnosed, non-metastatic cervical cancer patients treated in our hospital between January 2012 and November 2015 were screened to identify the study patients. The inclusion criteria were (1) age 18–70 years; (2) biopsy-confirmed diagnosis of cervical cancer; (3) no distant metastasis found on preoperative gynecological and imaging examination; (4) disease stage IB1 to IIA2 according to International Federation of Gynecology and Obstetrics 2009 (FIGO 2009); (5) treatment with radical hysterectomy and pelvic lymphadenectomy plus adjuvant radiotherapy at our hospital; (6) positive lymph nodes or parametrial invasion on post-operative pathological examination, or meeting Sedlis criteria; and (7) pathological type confirmed as adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma. The exclusion criteria were (1) positive/close vaginal stump (surgical margin of <5 mm, (15-17) on post-operative pathological examination; (2) receipt of radical chemoradiotherapy; (3) synchronous other cancers; (4) pregnancy or lactation; (5) a previous history of radiotherapy; or (6) incomplete surgical or radiotherapy data. Patients with positive parametrial margin were not excluded.

Tumor Staging and Surgery

Preoperatively, chest radiography, abdominal computerized tomography scan or ultrasonography, and pelvic plain and enhanced magnetic resonance imaging or whole-body 18F-FDG positron emission tomography were performed to exclude distant metastasis. An experienced gynecological oncologist with more than 10 years of clinical experience determined the stage of patients according to the FIGO 2009 staging classification.

Information was collected on pathological type, the number of positive/dissected lymph nodes, parametrial infiltration, vaginal stump involvement, depth of muscle invasion, tumor size, lymphovascular space invasion, and margin status.

Adjuvant Therapies

Post-operatively, all patients received adjuvant EBRT using a four-field pelvic irradiation technique. The treatment field generally extended from the lower edge of the obturator to L5. When lateral fields were used, the posterior border encompassed S3. The total dose delivered was 45–50.4 Gy in 25–28 fractions at 1.8 Gy/fraction. All patients received one fraction daily for 5 days per week. Patients with HRF also received cisplatin-based chemotherapy at a dose of 50–75 mg/m^2 once every 3 weeks.

There was no uniform standard for BT; the application of BT was mainly based on the treating physician's clinical experience and habits. The automatic driven γ ray after-loading device KC-HDR-C of Beijing Kelinzhong was used; this is a high-dose-rate after-loading device with a iridium-192 source. The prescribed dose was delivered at 5 mm depth from the mucosal surface. The 2-dimensional BT technique was used for all patients. The active length depended on the length of the vaginal stump, which ranged from 1.5 to 5.0 cm. BT was implemented immediately after the end of EBRT, and with a total dose of 12–18 Gy in 2–3 fractions at 6 Gy/fraction, 1 fraction daily over 1–2 days per week.

Variables Examined

The influence of different variables on survival outcomes after treatment were assessed; these variables included age (<45 vs. ≥45 years), FIGO2009 stage (IB1, IB2, IIA1, IIA2), comorbidities (hypertension or diabetes),

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

family history of any malignancy, chemotherapy, transfusion during treatment, pathological type, presence of HRF/IRF, the interval between surgery and radiotherapy, and duration of radiotherapy.

Follow-Up and Statistical Analysis

Patients were followed up every 3 months during the first 2 years, every 6 months during the next 2–3 years, and annually thereafter. Follow-up continued until death or April 1, 2020. The end points (time to the first defining event) were local-regional recurrence free survival (LRRFS) and overall survival (OS).

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY). The chi-square test was used to compare ordinal and categorical variables between groups. The LRRFS and OS rates were estimated using the Kaplan–Meier method, and differences in survival curves were compared by the log-rank test. The Cox proportional hazards model was used to evaluate the independent predictive value of different variables. Two-tailed $p < 0.05$ was considered significant.

Results

Patient Characteristics

Of the 319 patients initially identified, 94 were excluded (14 had incomplete information on radiotherapy or did not receive radiotherapy in our hospital; 23 had positive vaginal stumps; 24 had undergone surgery at some other hospital; 4 had incomplete pathological data; 6 had distant metastasis at diagnosis, and 23 had ineligible pathological types). Finally, 225 patients who met all eligibility criteria were enrolled. Of these 225 patients, 131 had HRF (positive lymph node or parametrial invasion). While all 131 patients had positive lymph nodes, 16 patients also had parametrial invasions. The median number of positive lymph nodes was 2 (range, 1–15). Nine patients had >10 positive lymph nodes. There were 193 patients with IRF (meeting Sedlis criteria). While 32 patients had HRF but no IRF, 94 had IRF alone (meeting Sedlis criteria), and 99 had both HRF and IRF. Of the 225 included patients, 99 received BT. Table 1 summarizes the patient characteristics.

Local-Regional Recurrence–Free Survival

The median follow-up was for 64 months (range, 7–96 months). Local-regional recurrence occurred in 45 patients (5 vaginal recurrences, 36 pelvic recurrences and 4 vaginal recurrences with pelvic relapse): 22 had isolated local-regional recurrence and 23 had local-regional recurrence plus distant metastases. While 13 local-regional recurrences occurred in patients receiving EBRT and BT, 32 local-regional recurrences occurred in patients receiving EBRT alone; the corresponding 5-year LRRFS rates were 87.7% and 72.5%, respectively ($p = 0.004$; Fig. 1).

In univariate analysis, BT, pathological type, HRF, transfusion, and duration of radiotherapy were significantly associated with LRRFS ($p < 0.05$). In multivariate analysis, the factors independently associated with LRRFS were BT (HR = 0.463, 95% CI = 0.232–0.924, $p = 0.029$), pathological type (HR = 3.190, 95% CI = 1.470–6.922, $p = 0.003$), HRF (HR = 4.034, 95% CI = 1.677–9.705, $p = 0.002$), transfusion (HR = 2.614, 95% CI = 1.414–4.832, $p = 0.002$), and duration of radiotherapy (HR = 2.035, 95% CI = 1.020–4.058, $p = 0.044$). Table 2 summarizes the results of univariate and multivariate analyses.

Patients with IRF were more likely to receive BT than those with HRF alone (Table 1). Analysis after stratification by HRF and IRF showed that patients with HRF did not benefit from BT ($p = 0.098$), while patients with IRF but no HRF did ($p = 0.044$). Patients with IRF, with or without HRF, benefited from BT ($p = 0.017$) while patients with HRF alone did not ($p = 0.078$). Table 3 summarizes the results.

Overall Survival

OS events occurred in 46 (20.44%) patients; 15 (6.67%) occurred in the group receiving EBRT and BT, and 31 (13.78%) occurred in the group receiving EBRT alone; the corresponding 5-year OS rates were 78.4% and 75.3%, respectively ($p = 0.055$; Fig. 1).

In univariate analysis, pathological type, HRF, and transfusion were significantly associated with OS, while BT ($p = 0.055$) and duration of radiotherapy ($p = 0.060$) were not. In multivariate analysis, BT was not independently associated with improved OS ($p = 0.237$, HR = 0.684, 95% CI = 0.365–1.283). Table 2 summarizes the results. In subgroup analysis, BT did not show OS benefit in any subgroup (Table 3).

Toxicity

Grade 3–4 bone marrow depression occurred in 28 (12.4%) patients: 18 patients with BT and 10 without. Other grade 3 or higher adverse effects occurred in 7 patients: 2 patients receiving EBRT plus BT and 5 patients receiving EBRT alone. These adverse effects included ureteral stricture/obstruction requiring surgical intervention (5 patients) and death (2 patients). Among the five patients developing ureteral stricture/obstruction, one patient who did not receive BT had a sigmoid colon fistula. Of the two patients who died, one died of volvulus half a year after treatment and one died of gastrointestinal hemorrhage one year after treatment. Both deaths were in the group receiving EBRT alone. In addition, 6 patients

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

Table 1
Characteristics of the 225 patients enrolled in this study.

	Brachytherapy		*p value*[b]
	Yes (n = 99)	No (n = 126)	
Age (years)	No. (%)	No. (%)	1.000
<45	33 (33.3)	42 (33.3)	
≥45	66(66.7)	84 (66.7)	
Stage (FIGO 2009)			0.934
IB1	26	36	
IB2	30	40	
IIA1	15	19	
IIA2	28	31	
Complications			0.499
Yes	25 (24.2)	27 (21.4)	
No	74 (76.8)	99 (78.6)	
Family history			0.461
Yes	7 (7.1)	6 (4.8)	
No	92 (92.9)	120 (95.2)	
Chemotherapy			0.595
Yes	67 (67.7)	81 (64.3)	
No	32 (32.3)	45 (35.7)	
Histology[a]			0.167
Squamous cell carcinoma	92 (92.9)	110 (87.3)	
Adenocarcinoma	7 (7.1)	16 (12.7)	
High risk factor			0.004
Yes	45 (45.5)	86 (68.3)	
No	54 (54.5)	40 (31.7)	
Intermediate risk factor			0.019
Yes	91 (91.9)	102 (81.0)	
No	8 (8.1)	24 (19.0)	
Transfusion			0.441
Yes	26	39	
No	73	87	
Period between surgery and radiotherapy (days)			0.336
<29	48 (48.5)	53 (42.1)	
≥29	51 (51.5)	73 (57.9)	
Duration of radiotherapy (days)			0.649
<39	41 (41.4)	56 (44.4)	
≥39	58 (58.6)	70 (55.6)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics.
[a] Adenosquamous carcinoma was classified as squamous cell carcinoma.
[b] *p*-values were calculated using the χ^2 test.

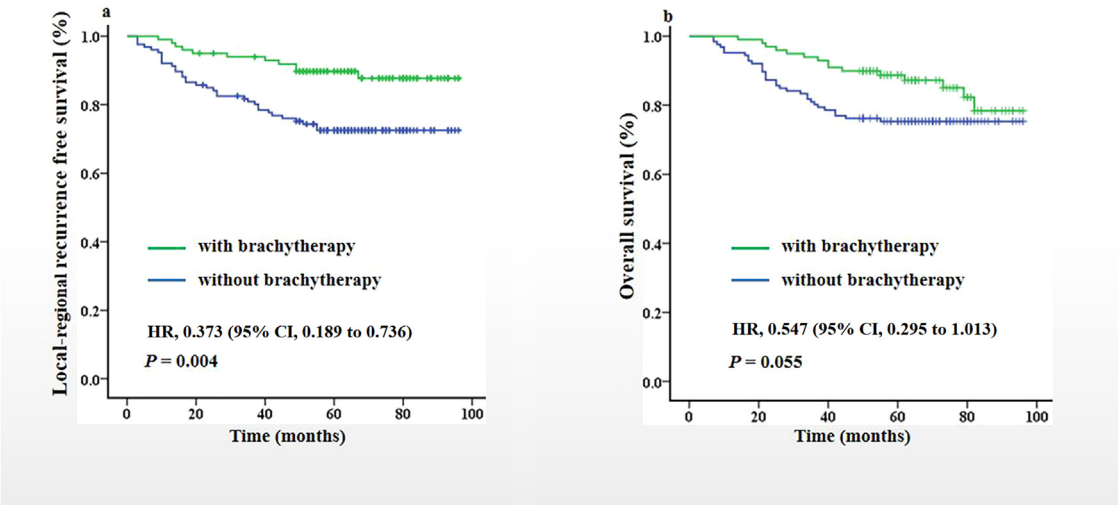

Fig. 1. Five-year local-regional recurrence–free survival curve (a) and overall survival curve (b) for the 225 post-operative cervical cancer patients receiving external beam radiotherapy with or without brachytherapy.

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

Table 2
Results of univariate and multivariate analyses for local-regional recurrence–free survival and overall survival.

Variables	Univariate analysis (LRRFS)		Multivariate analysis (LRRFS)		Univariate analysis (OS)		Multivariate analysis (OS)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Brachytherapy	0.373 (0.189–0.736)	0.004	0.463 (0.232–0.924)	0.029	0.547 (0.295–1.013)	0.055	0.684 (0.365–1.281)	0.235
Histology[a]	2.919 (1.404–6.067)	0.004	3.189 (1.470–6.921)	0.003	3.098 (1.492–6.434)	0.002	3.646 (1.687–7.879)	0.001
High risk factor	5.341 (2.260–12.624)	0.001	4.028 (1.673–9.698)	0.002	3.812 (1.778–8.174)	0.001	3.339 (1.532–7.276)	0.002
Duration of radiotherapy	2.559 (1.296–5.051)	0.007	2.021 (1.007–4.055)	0.048	1.829 (0.976–3.430)	0.060	1.493 (0.784–2.842)	0.223
Transfusion	2.384 (1.327–4.284)	0.004	2.631 (1.415–4.890)	0.002	2.196 (1.227–3.930)	0.008	2.437 (1.319–4.505)	0.004
Stage (FIGO 2009)	1.000 (0.779–1.284)	0.012	0.980 (0.757–1.270)	0.879	1074 (0.840–1.372)	0.051	1.038 (0.806–1.336)	0.773
Intermediate risk factor	0.713 (0.332–1.531)	0.386			0.627 (0.302–1.298)	0.208		
Chemotherapy	1.064 (0.539–2.100)	0.858			1.053 (0.534–2.079)	0.881		
Age	1.249 (0.656–2.380)	0.499			1.249 (0.656–2.380)	0.499		
Complications	0.807 (0.389–1.676)	0.565			0.826 (0.398–1.714)	0.608		
Family history	1.204 (0.373–3.887)	0.756			1.775 (0.634–4.969)	0.275		
Period between surgery and radiotherapy	0.686 (0.382–1.232)	0.207			0.669 (0.374–1.196)	0.175		

Abbreviations: LRRFS = local-regional recurrence free survival; OS = overall survival; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; CI = confidence interval.
[a] Adenosquamous carcinoma was classified as squamous cell carcinoma.

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

Table 3
Stratified analysis for 5-year local-regional recurrence–free survival and overall survival by high risk factors and intermediate risk factors.

	LRRFS (months, 95%CI)			OS (months, 95%CI)		
	EBRT and BT (n = 99)	EBRT alone (n = 126)	*P*	EBRT and BT (n = 99)	EBRT alone (n = 126)	*p*
Total	88.46 (84.17–92.76)	76.32 (70.51–82.12)	0.003	86.86 (82.54–91.17)	78.56 (73.13–83.99)	0.055
High risk factor[a]						
Yes (n = 131)	79.27 (71.49–87.05)	70.55 (62.84–78.27)	0.098	79.46 (72.31–86.60)	72.94 (65.63–80.25)	0.208
No (n = 94)	95.03 (93.17–96.90)	86.39 (79.98–92.79)	0.044	91.93 (88.04–95.82)	88.37 (83.06–93.67)	0.453
Intermediate risk factor[b]						
Yes (n = 193)	-	-	0.017	87.18 (82.69–91.68)	79.81 (74.05–85.58)	0.068
No (n = 32)	-	-	0.078	72.71 (63..47–1.94)	73.25 (58.90–87.61)	0.737

Abbreviations: LRRFS = local-regional recurrence free survival; OS = overall survival; CI=confidence interval; BT = brachytherapy; EBRT = external beam radiation therapy.
[a] "Yes" means the patients with high risk factor(s), no matter the intermediate risk factor; "No" means the patients meeting the Sedlis criteria alone.
[b] "Yes" means the patients meeting the Sedlis criteria, no matter the high risk factor; "No" means the patients with high risk factor(s) alone.

developed chronic lower limb swelling due to damage to lymphatic drainage.

Discussion

BT is irreplaceable boost for EBRT in the treatment of locally advanced cervical cancer (3,11). However, for post-operative patients, the role of BT remains unclear. For those with risk factors, there is no agreement on whether BT is necessary following EBRT. In clinical practice, for patients with risk factors, the application of BT generally depends on the preference of the treating physician. In a retrospective analysis of 1719 cervical cancer patients with positive surgical margins treated with adjuvant radiation therapy, the 3-year OS was significantly better with the combination of EBRT and BT than with EBRT alone (79.8% vs. 71.9%, $p < 0.001$). Unexpectedly, only 45.3% of patients in the study received BT (12). In another study, excellent survival outcomes were obtained by adding vaginal BT to simple hysterectomy and EBRT for patients with early cervical cancer (18). In our study, we excluded patients with positive stump who have already been proven to benefit from BT. All of our patients had HRF and/or IRF and received adjuvant EBRT. We found significantly better LRRFS in patients receiving EBRT plus BT than in those receiving EBRT alone. This result was consistent with some previous researches that found the addition of BT improved outcomes in risk patients (13,19). Gultekin et al. found adding BT to EBRT did not provide any benefit in local control or survival, but in their study, patients receiving BT had worse prognostic factors than the EBRT alone group (20). Ohara et al. found that among patients who had received post-operative radiotherapy, 41% failed in the pelvis, mainly at the vaginal wall and vaginal cuff (21). Vaginal brachytherapy allows for a high dose to the tumor bed and may eradicate the microscopic residual tumors, which might reduce the pelvic failure. In multivariate analysis, we found that the independent predictors of worse LRRFS included, in addition to lack of BT, pathological type (adenocarcinoma), HRF, a longer period of radiation, and blood transfusion during treatment. The adverse impact of these factors on survival has been reported previously (22–25).

In subgroup analysis, receipt of BT was associated with improved LRRFS in patients having IRF with or without HRF. Sedlis criteria reflect the local characteristics of cervical cancer patients. The risk of recurrence is significantly higher if the tumor size is over 4 cm or if there is tumor infiltration of the full cervical wall; further, most recurrences occur in the pelvic cavity (26). Thus, patients with IRF can benefit significantly from adjuvant radiotherapy with increased pelvic dose (4,5). However, whether the addition of BT to EBRT is beneficial in this setting is unknown. Some studies have shown that BT can boost the pelvic dose for patients with IRF without causing unacceptable side effects (9,14,27). In GOG263, which assessed the addition of chemotherapy to radiation therapy in patients with IRF, BT was specially prohibited (28). Our study proves that BT can improve LRRFS for patients with IRF.

For patients with HRF, the NCCN guidelines do not recommend BT, but one large retrospective study has demonstrated a survival benefit in patients with positive stump (12). A previous study that assessed the effect of BT in pelvic node–positive IB1-IIA2 cervical cancer patients found that the addition of BT significantly improved 5-year progression-free survival and that the most common site of relapse was the pelvis in patients not receiving BT (26). In our study, the addition of BT did not provide any overall survival advantage for patients having HRF, with or without IRF. Previous studies have shown that, for cervical cancer patients with parametrial infiltration or positive regional lymph nodes, vaginal BT only provides a limited increase of dose to the parametrial area, and patients with positive lymph nodes have a high risk of distant metastasis (29–31). In our study, while BT did improve the LRRFS of these patients, the improvement was not statistically significant.

In our study, patients receiving BT tended to achieve a better 5-year OS than patients not receiving BT, but the difference was not statistically significant. Subgroup anal-

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

ysis showed that BT did not significantly improve OS for patients with HRF or IRF. This result is consistent with previous studies that found that BT did not improve the OS of post-operative patients with positive pelvic lymph nodes (26). Li et al., too, found no significant OS benefit with the addition of BT to EBRT in patients with negative surgical margins (12); however, patients receiving EBRT plus BT tended to have better OS than patients receiving EBRT alone. The explanation could be that the significantly better LRRFS in patients with IRF affected the OS rates (the subgroup with IRF formed a large proportion of the total cohort). Fajardo et al., however, reported that adjuvant BT can improve the OS of high-risk patients (13). This conflicting result could be because Fajardo et al. attributed the survival advantage to the addition of vaginal vault BT boost between the earlier and later recruits; however, they could not completely exclude the influence of improved radiotherapy technique and the addition of chemotherapy.

The incidence of grade 3–4 acute hematological toxicities (28/225) was lower in our study than in other studies (32), probably because some of our patients did not receive chemotherapy. The incidence of severe chronic side effects was lower in our study than in the study by Smith et al. (18). As the authors suggested, retrospective studies tend to underestimate the incidence of complications because many facilities do not have accurate records of the medical care that patients receive after completing cancer treatment (18). However, our finding that BT will not increase serious chronic side effects is relatively reliable as ours was a single-center study with regular follow-up. Some patients develop chronic lower limb edema many years after the completion of radiotherapy; this deserves more attention as the consequently impaired mobility can have a serious impact on quality of life.

This study found that vaginal BT can improve the LRRFS for early post-operative cervical cancer patients with risk factors other than positive stump; further, the results of subgroup analysis suggest that BT provides benefits in patients with IRF but not in those with HRF. This study may provide a reference for future clinical trials and for daily clinical practice. However, due to the retrospective and single-institution nature of this study, the results need to be verified by further prospective studies.

Conclusions

Brachytherapy can improve local-regional recurrence-free survival following radical hysterectomy and external beam radiation therapy for early-stage cervical cancer patients meeting Sedlis criteria; the side effects appear to be tolerable.

References

[1] Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics. *CA Cancer J Clin 2022* 2022;72:7–33. doi:10.3322/caac.21708.

[2] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–E386. doi:10.1002/ijc.29210.

[3] National Comprehensive Cancer Network. NCCN Guidelines: Cervical cancer. Version 1.2021.

[4] Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. *Gynecol Oncol* 1999;73:177–183. doi:10.1006/gyno.1999.5387.

[5] Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation inStage IB cervical carcinoma with poor prognostic features: follow-up of agynecologic oncology group study. *Int J Radiat Oncol Biol Phys* 2006;65:169–176. doi:10.1016/j.ijrobp.2005.10.019.

[6] Cusimano MC, Baxter NN, Gien LT, et al. Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer. *Am J Obstet Gynecol* 2019;221:619.e1–619.e24. doi:10.1016/j.ajog.2019.07.009.

[7] Matsuo K, Novatt H, Matsuzaki S, et al. Wait-time for hysterectomy and survival of women with early-stage cervical cancer: a clinical implication during the coronavirus pandemic. *Gynecol Oncol* 2020;158:37–43. doi:10.1016/j.ygyno.2020.05.019.

[8] Perez CA, Grigsby PW, Camel HM, et al. Irradiation alone or combined with surgery in stage IB, IIA, and IIB carcinoma of the uterine cervix: update of a nonrandomized comparison. *Int J Radiat Oncol Biol Phys* 1995;31:703–716. doi:10.1016/0360-3016(94)00523-0.

[9] Kim YJ, Lee KJ, Park KR, et al. Prognostic analysis of uterine cervical cancer treated with postoperative radiotherapy: importance of positive or close parametrial resection margin. *Radiat Oncol* 2015;J33:109–116. doi:10.3857/roj.2015.33.2.109.

[10] Abe A, Matoda M, Okamoto S, et al. Resection of the vaginal vault for vaginal recurrence of cervical cancer after hysterectomy and BT. *World J Surg Oncol* 2015;13:137. doi:10.1186/s12957-015-0495-8.

[11] Campitelli M, Lazzari R, Piccolo F, et al. Brachytherapy or external beam radiotherapy as a boost in locally advanced cervical cancer: a Gynaecology Study Group in the Italian Association of Radiation and Clinical Oncology (AIRO) review. *Int J Gynecol Cancer* 2021;31:1278–1286. doi:10.1136/ijgc-2020-002310.

[12] Li R, Shinde A, Chen YJ, et al. Survival benefit of adjuvant BT after hysterectomy with positive surgical margins in cervical cancer. *Int J Radiat Oncol Biol Phys* 2018;102:373–382. doi:10.1016/j.ijrobp.2018.05.076.

[13] Dávila Fajardo R, van Os R, Buist MR, et al. Post-operative radiotherapy in patients with early stage cervical cancer. *Gynecol Oncol* 2014;134:52–59. doi:10.1016/j.ygyno.2014.04.045.

[14] Wang H, Zhu L, Lu W, et al. Clinicopathological risk factors for recurrence after neoadjuvant chemotherapy and radical hysterectomy in cervical cancer. *World J Surg Oncol* 2013;11:301. doi:10.1186/1477-7819-11-301.

[15] Estape RE, Angioli R, Madrigal M, et al. Close vaginal margins as a prognostic factor after radical hysterectomy. *Gynecol Oncol* 1998;68:229–232. doi:10.1006/gyno.1998.4960.

[16] Viswanathan AN, Lee H, Hanson E, et al. Influence of margin status and radiation on recurrence after radical hysterectomy in stage 1B cervical cancer. *Int J Radiation Oncology Biol Phys* 2006;5:1501–1507. doi:10.1016/j.ijrobp.2006.03.010.

[17] McCann GA, Taege SK, Boutsicari CE, et al. The impact of close surgical margins after radical hysterectomy for early-stage cervical cancer. *Gynecol Oncol* 2013;128:44–48. doi:10.1016/j.ygyno.2012.10.028.

[18] Smith KB, Amdur RJ, Yeung AR, et al. Postoperative radiotherapy for cervix cancer incidentally discovered after a simple hysterectomy for either benign conditions or noninvasive pathology. *Am J Clin Oncol* 2010;33:229–232. doi:10.1097/COC.0b013e3181a6500d.

[19] Lan ML, Yu X, He X, et al. Comparison of chemoradiotherapy with

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002

and without brachytherapy as adjuvant therapy after radical surgery in early-stage cervical cancer with poor prognostic factors. *Medicine (Baltimore)* 2017;96:e8384. doi:10.1097/MD.0000000000008384.

[20] Gultekin M, Esen CSB, Balci B, et al. Role of vaginal brachytherapy boost following adjuvant external beam radiotherapy in cervical cancer: Turkish Society for Radiation Oncology Gynecologic Group Study (TROD 04-002). *Int J Gynecol Cancer* 2021;31:185–193. doi:10.1136/ijgc-2020-001733.

[21] Ohara K, Tsunoda H, Nishida M, et al. Use of small pelvic field instead of whole pelvic field in postoperative radiotherapy for node-negative, high-risk stages I and II cervical squamous cell carcinoma. *Int J Gynecol Cancer* 2003;13:170–176. doi:10.1046/j.1525-1438.2003.13014.x.

[22] Connor JP, O'Shea A, McCool K, et al. Peri-operative allogeneic blood transfusion is associated with poor overall survival in advanced epithelial ovarian cancer; potential impact of patient blood management on cancer outcomes. *Gynecol Oncol* 2018;151:294–298. doi:10.1016/j.ygyno.2018.08.040.

[23] Pushan Z, Manbiao C, Sulai L, et al. The impact of perioperative blood transfusion on survival and recurrence after radical prostatectomy for prostate cancer: a systematic review and meta-analysis. *J Cancer Res Ther* 2018;14:S701–S707. doi:10.4103/0973-1482.193115.

[24] Shaverdian N, Gondi V, Sklenar KL, et al. Effects of treatment duration during concomitant chemoradiation therapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2013;86:562–568. doi:10.1016/j.ijrobp.2013.01.037.

[25] Jhawar S, Hathout L, Elshaikh MA, et al. Adjuvant chemoradiation therapy for cervical cancer and effect of timing and duration on treatment outcome. *Int J Radiat Oncol Biol Phys* 2017;98:1132–1141. doi:10.1016/j.ijrobp.2017.03.045.

[26] Li L, Kou X, Feng X, et al. Postoperative external beam irradiation with and without BT in pelvic node-positive IB1-IIA2 cervical cancer patients: a retrospective clinical study. *Radiat Oncol* 2015;10:189. doi:10.1186/s13014-015-0495-4.

[27] Noh JM, Park W, Kim YS, et al. Comparison of clinical outcomes of Adenocarcinoma and Adenosquamous carcinoma in uterine cervical cancer patients receiving surgical resection followed by radiotherapy: a multicenter retrospective study (KROG 13-10). *Gynecol Oncol* 2014;132:618–623. doi:10.1016/j.ygyno.2014.01.043.

[28] Gynecologic Oncology Group. Radiation therapy with or without chemotherapy in patients with stage I or stage II cervical cancer who previously underwent surgery. NLM Identifier: NCT01101451. Available at: https://clinicaltrials.gov/ct2/show/NCT01101451. Accessed November 13, 2017.

[29] Lee YJ, Kim DY, Lee SW, et al. A postoperative scoring system for distant recurrence in node-positive cervical cancer patients after radical hysterectomy and pelvic lymph node dissection with para-aortic lymph node sampling or dissection. *Gynecol Oncol* 2017;144:536–540. doi:10.1016/j.ygyno.2017.01.001.

[30] Matsuo K, Shimada M, Aoki Y, et al. Comparison of adjuvant therapy for node-positive clinical stage IB-IIB cervical cancer: systemic chemotherapy versus pelvic irradiation. *Observ Study Int J Cancer* 2017;141:1042–1051. doi:10.1002/ijc.30793.

[31] Matsuo K, Nusbaum DJ, Machida H, et al. Populational trends and outcomes of postoperative radiotherapy for high-risk early-stage cervical cancer with lymph node metastasis: concurrent chemo-radiotherapy versus radiotherapy alone. *Am J Obstet Gynecol* 2020;222:484.e1–484.e15. doi:10.1016/j.ajog.2019.10.010.

[32] Wang X, Zhao Y, Shen Y, et al. Long-term follow-up results of simultaneous integrated or late course accelerated boost with external beam radiotherapy to vaginal cuff for high risk cervical cancer patients after radical hysterectomy. *BMC Cancer* 2015;15:257. doi:10.1186/s12885-015-1248-3.

Please cite this article as: X.-L. Yu *et al.*, Role of brachytherapy in post-operative cervical cancer patients with risk factors other than positive stump, Brachytherapy, https://doi.org/10.1016/j.brachy.2022.10.002