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Stereotactic Body Radiation Therapy Boost in Patients With Cervical Cancer Ineligible for Brachytherapy

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Abstract. *Background: Standard treatment for locally advanced cervical cancer is external beam radiotherapy followed by brachytherapy (BT). Stereotactic body radiation therapy (SBRT) is a possible option for treating patients ineligible for BT. Patients and Methods: From October 2012 to July 2020, nine women with cervical cancer received SBRT to high-risk volumes. The Kaplan–Meier method was used to estimate the rates of overall and disease-free survival. Results: The median age was 52 years; 88% of patients had squamous carcinoma. Reasons for forgoing BT were cervical canal stenosis, treatment refusal and hematological disease. The median boost dose was 18 Gy and the median dose per fraction was 6 Gy. Median follow-up was 16 months. The median survival was 24 months, the actuarial 2-year OS rate was 70%, and median disease-free survival was 11 months. One grade 3 late vaginal toxicity was reported. No acute nor late grade 4 toxicities were observed. Conclusion: SBRT boost in patients with cervical cancer ineligible for BT led to acceptable survival outcomes and a safe toxicity profile.*

External beam radiotherapy (EBRT) with concurrent chemotherapy followed by intracavitary interventional radiotherapy/brachytherapy (BT) is the standard of care for patients with locally advanced cervical cancer (1-4). For these patients both intracavitary and interstitial BT are important components of the standard treatment (5-9). In daily clinical practice, however, a small proportion of patients refuse BT or are ineligible due to anatomical conditions not allowing the insertion of an applicator. The use of EBRT boost instead of BT was associated with quite unsatisfactory outcomes in several series of patients with locally advanced cervical cancer (10-13).

Stereotactic body radiation therapy (SBRT) can deliver high-dose radiation to the target volume in a very conformal manner over a few fractions and may be used in different clinical scenarios to treat the final boost volume in gynecological patients who are ineligible for BT, using non-uniform treatment schedule (14-16). SBRT might therefore represent an option for patients with locally advanced cervical cancer unfit for BT boost. Data on such an approach are scarce in literature, limited in numbers and use heterogeneous schedule of treatments (17-26). Therefore, the purpose of this study was to evaluate clinical results and acute and late toxicities of SBRT boost in a series of nine patients ineligible for BT at our Institute.

Patients and Methods

Patients. From October 2012 to July 2020, nine consecutive women with locally advanced cervical cancer were treated with SBRT as a final boost to the volumes considered at high-risk for relapse. Patient ages ranged from 38 to 79 years (median=57 years). Patient, tumor, and treatment characteristics are summarized in Table I. Patients were staged according to latest International Federation of Gynecology and Obstetrics (FIGO) criteria (27): Three had stage IIA, two stage IIB, one stage IIIB, one IIIC and two IV A. All patients were staged with total body computed tomography or positron-emission tomography/computed tomography (CT) and pelvic magnetic resonance imaging (MRI).

Treatments. Simulation CT images for both treatments were taken in 3-mm increments over the region of interest. Before simulation CT, all nine patients were asked to have an empty rectum (a micro enema was suggested before every boost fraction) and an empty bladder.

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Key Words: SBRT boost, cervical cancer, cervix, radiotherapy, stereotactic, brachytherapy.

Table I. *Patient characteristics*.

Patient	Age, years	Diagnosis	Histology	Stage (FIGO)	Recommended	Chemotherapy	EBRT dose, Gy/fractions	Reason ineligible for BT	SBRT boost dose, Gy/fractions
1	79	Cervix	SCC	IIIC	CHT + EBRT+ BT	None	61.6/28	Patient refusal	20/4
2	50	Cervix	SCC	IIB	CHT + EBRT+ BT	Cisplatin	61.6/28	Patient refusal	21/3
3	67	Cervix	SCC	IIB	CHT + EBRT+ BT	Cisplatin	60/30	Cervical stenosis	18/3
4	75	Cervix	SCC	IIA	CHT + EBRT+ BT	Cisplatin	61.6/28	Cervical stenosis	21/3
5	38	Cervix	SCC	IIA	CHT + EBRT+ BT	Cisplatin	61.6/28	Glanzmann's thrombasthenia	15/3
6	57	Cervix	SCC	IVA	CHT + EBRT+ BT	Cisplatin	61.6/28	Cervical stenosis	15/3
7	50	Cervix	SCC	IVA	CHT + EBRT+ BT	Carboplatin	61.6/28	Thrombocytopenia	15/3
8	58	Cervix	SCC	IIIB	CHT + EBRT+ BT	Cisplatin	61.6/28	Cervical stenosis	18/3
9	46	Cervix	ADC	IIA	TAH-BSO + EBRT + BT	Cisplatin	50.4/28	Cervical stenosis	25/5

ADC: Adenocarcinoma; BT: brachytherapy; EBRT: external beam radiation therapy; SCC: squamous cell carcinoma; TAH-BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Eight out of the nine patients were treated with simultaneous integrated boost (SIB) fractionated radiotherapy; seven of these patients were treated with prophylactic dose of 50.4 Gy (1.8 Gy per fraction) to the uterus/ovaries, and draining lymph-nodal groups according to internal and international guidelines, while the prescribed dose to the gross tumor volume (*i.e.* cervix, parametria, vaginal tissues based on vaginal extension) and involved lymph nodes was 61.6 Gy (2.2 Gy per fraction) (4, 28, 29). One of these eight patients was treated with a prophylactic dose of 54 Gy (2 Gy per fraction) and a total dose to the GTV of 60 Gy (2 Gy per fraction). One patient received standard fractionation to the pelvis with a total dose of 50.4 Gy (1.8 Gy per fraction).

Eight patients were treated with chemotherapy during fractionated EBRT: 40 mg/m^2 cisplatin weekly for 5-6 cycles. Chemotherapy began within the first week of radiotherapy start and was administered during EBRT treatment but not during the boost. One patient received only radiotherapy with intensity-modulated radiotherapy (IMRT) SIB technique.

Pelvic MRI was performed in all patients after completing EBRT to assess the radiologic response. T2-Weighted axial acquisition was chosen as image fusion to better draft the target volumes.

The clinical tumor volume (CTV) and organs at risk (OARs) were contoured on sequential axial CT slices.

For patients achieving local complete radiological response after EBRT, the high-risk (HR)-CTV) was defined as the whole cervix. For patients having residual tumor after EBRT, the HR-CTV included the residual GTV and the whole cervix. The planning target volume (PTV) was created expanding the HR-CTV by 5 mm in all directions, except in the posterior direction where a reduced margin of 3-4 mm was employed in order to reduce the dose to the rectal wall. The OARs included the rectum, sigmoidal colon, urinary bladder, and bowel.

The Eclipse 4.5.5 (Varian) treatment planning system, and volumetric-modulated arc therapy/intensity-modulated radiotherapy/IMRT technique on a 6-MV linear accelerator Varian were used for SBRT (Figure 1). All patients underwent image-guided radiotherapy using cone-beam CT system as daily pre-treatment imaging. Any observed set-up error ≥2 mm was corrected prior to treatment.

The patients were treated with a stereotactic boost with a total dose of 15-25 Gy in 3-5 fractions (5-7 Gy per fraction). Radiotherapy was delivered every 72 h according to the high dose-rate BT schedule usually used. The different fractionated schedules adopted were tailored for each patient with the aim of a dose to the OAR-adapted approach, respecting the prescribed oncological dose to the tumor, where the total dose was calculated according to doses to PTV equivalent dose in 2 Gy fractions (EQD2) (80.8-92.4 Gy) and to OARs (dose max of 75 Gy EQD2 to 2cc of rectum and dose max of 90 Gy to 2cc of bladder) according to International Commission on Radiation Units and Measurements 89 (30).

Toxicities and follow-up. Urinary and lower gastrointestinal acute adverse effects were reported according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer scoring system (31) every week during EBRT and SBRT, 5-6 weeks and 3 months after treatment completion, with late toxicity being reported after a minimum 6-month follow-up period. Sexual late toxicities were scored after a minimum 6-month follow-up period according to the Symptoms, Objective, Management, Analytic scoring system (32). Patients were followed-up with clinical examinations, blood tumor markers and pelvic MRI performed at 2 months after boost and every 3 months thereafter. Total body positron-emission tomography-CT scan or transvaginal ultrasound were prescribed depending on clinical status and disease stage.

Response. Response was assessed with pelvic MRI immediately after completing EBRT and the end of SBRT boost according to RECIST 1.1 criteria (33).

Statistical analysis. Statistical analysis was performed using the SPSS statistical software package version 13.0 (SPSS, Chicago, IL, USA). Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Disease-free survival (DFS) was calculated from the date of the end of radiotherapy course to the date of either distant metastases, locoregional recurrence or the date of the last follow-up. The Kaplan–Meier method was used to estimate the rates of OS and DFS.

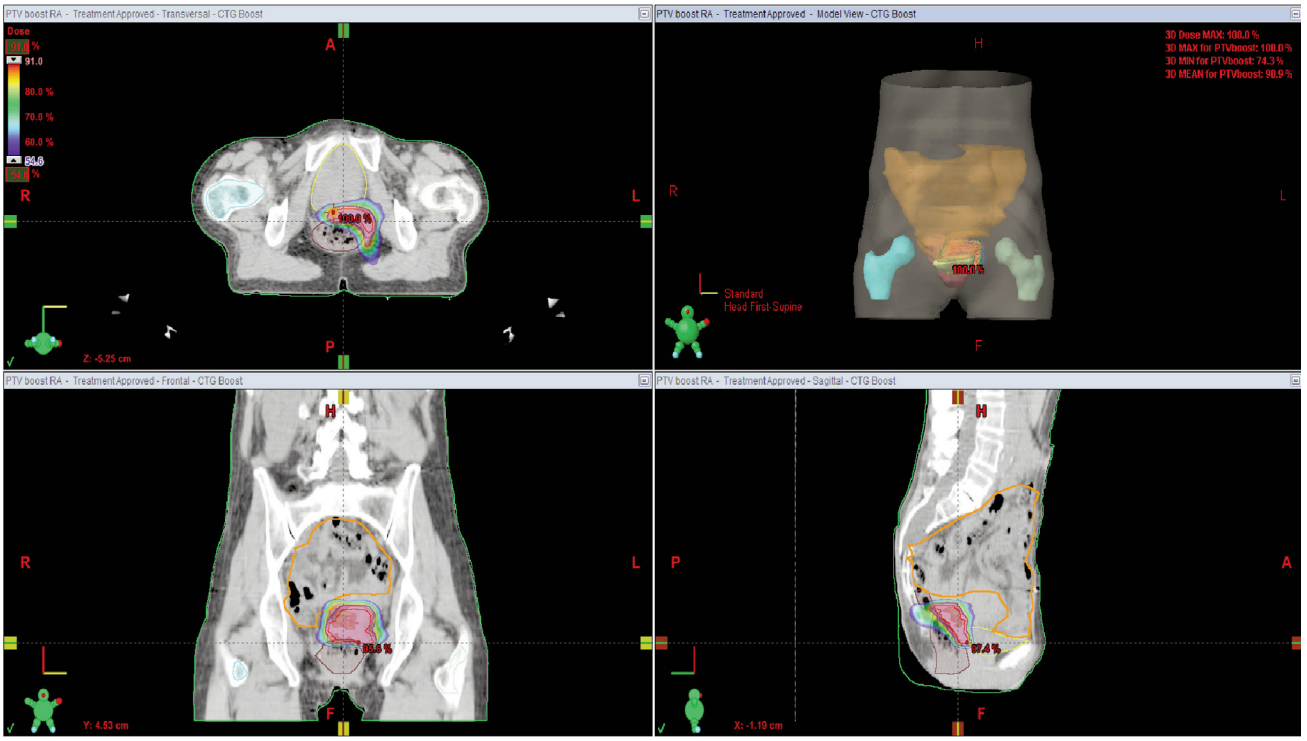

Figure 1. *Stereotactic body radiation therapy boost with the Eclipse 4.5.5 (Varian) treatment planning system for a woman unfit for brachytherapy.*

Results

A total of nine patients were included in the analysis. The median age was 52 (range=38-79) years. The majority of patients (88%) had squamous cell carcinoma. The most frequent reason for forgoing BT was cervical canal stenosis (six patients). Patient and tumor characteristics are shown in Table I.

Four out of nine patients showed complete radiological response and five patients had gross residual tumor assessed by pelvic MRI performed after EBRT before SBRT boost.

The median time between the end of EBRT and the start of the SBRT boost was 20 days (range=14-30 days). The median boost dose for patients was 18 Gy (range=15-25 Gy); the median dose per fraction was 6 Gy (range=5-7 Gy). Treatments were prescribed to the median 94% isodose line (range=91-98%). The median PTV was 63.9 (range=19.3-141.4) cm^3 (Table II). The median total dose was 84 Gy (range=80.8-92.4 Gy EQD2) delivered in an overall median treatment time of 92 days (range=62-104 days).

Response was assessed with pelvic MRI after a median of 3 months (range=2-5 months) from the end of SBRT boost. After SBRT boost, complete response was recorded in all patients. Only one local recurrence was observed at 8 months after SBRT boost in a patient with FIGO stage IVA at diagnosis who had gross residual tumor after EBRT but achieved complete radiological response after SBRT boost. The systemic progression of metastatic disease was seen in two patients with FIGO stage IIIB and IVA respectively, who did not achieve complete response after EBRT but achieved local complete response after SBRT boost. One patient died 13 months after SBRT boost completion from noncancer causes (Table III). The median follow-up was 16 months (range=6-58 months). The median OS was 24 months (range=11-65 months) and the actuarial 2-year OS rate was 70%. The median DFS was 11 months (range=2-30 months) (Figure 2).

The maximum rectal point dose ranged from 6.4 to 23.5 Gy (median=15.7) and the maximum bladder point dose ranged from 12.5 to 24 Gy (median=16.5 Gy). Acute grade 1 bladder toxicity was reported in two out of nine (22%) patients, grade 1-2 vaginal toxicity was not reported, and there was one case (11%) of grade 1 gastrointestinal toxicity observed. Late vaginal toxicities were reported as follows: Grade 1 in two patients (22%), grade 2 in one (11%) and grade 3 in one (11%). Grade 2 late urinary and gastrointestinal toxicities were reported in two of nine patients (22%). No evidence of grade 4 bladder, vaginal, or gastrointestinal toxicities were noted.

Table II. *Dosimetric data*.

Patient	EBRT technique	EBRT dose, Gy/ fractions	Boost technique	Boost dose, Gy/ fractions	Boost isodose, Gy	PTV, cm^3	EBRT+ SBRT, EQD2 Gy	Bladder dose, Gy				Rectal dose, Gy			
								Dmax	Dmean	D2cc	D5cc	Dmax	Dmean	D2cc	D5cc
1	IMRT-SIB	61.6/28	SBRT	20/4	97	25.4	87.6	19.6	6.3	18.9	16.2	19.2	4	17.4	15.1
2	IMRT-SIB	61.6/28	SBRT	21/3	94	28.9	92.4	18.7	8.4	20.1	15,7	18.6	3.6	13.2	9.2
3	VMAT	60/30	SBRT	18/3	94	19.3	84	13	3.2	10.5	9.3	10.8	2.4	5.8	5.1
4	IMRT-SIB	61.6/28	SBRT	21/3	94	24.1	92.4	18.5	5	15.3	13.2	15.7	3.8	11.1	8.8
5	VMAT	61.6/28	SBRT	15/3	92	94	81.4	12.5	7	11.5	12.5	6.4	1.8	4.3	3.6
6	IMRT-SIB	61.6/28	SBRT	15/3	98	63.9	81.4	14.8	7.8	14.7	13.8	14.8	5.8	14.6	13.2
7	IMRT-SIB	61.6/28	SBRT	15/3	98	141.4	81.4	14.7	3.9	14.6	14.3	14.9	4.8	14.8	14.6
8	IMRT-SIB	61.6/28	SBRT	18/3	96	78.4	86.6	16.5	7.5	13.6	17.8	16.7	7.5	13.2	12.3
9	IMRT	50.4/28	SBRT	25/5	91	68.3	80.8	24	7.5	19.4	15.4	23.5	5.8	23.3	22.9

BT: Brachytherapy; D2cc: dose to 2cc; D5cc: dose to 5cc; Dmax: maximum dose; Dmean: mean dose; EBRT: external beam radiation therapy; EQD2: equivalent dose in 2 Gy fractions; IMRT-SIB: simultaneous integrated boost by intensity-modulated radiotherapy; OAR: organ at risk; PTV: planning target volume; VMAT: volumetric-modulated arc therapy.

Table III. *Patient imaging data and outcomes*.

Patient	FIGO stage	MRI post EBRT	SBRT dose, Gy/fractions	MRI post SBRT	LC (months after SBRT)	MFS (months after SBRT)	Status (at last FU)
1	IIIC	PR	15/3	CR			Dead of other cause
2	IIB	CR	14/2				Alive, no disease
3	IIB	CR	12/2				Alive, no disease
4	IIA	CR	21/3				Alive, no disease
5	IIA	CR	15/3				Alive, no disease
6	IVA	PR	15/3	CR	Recurrence (8)		Dead due to cancer
7	IVA	PR	15/3	CR		PD (2)	Dead due to cancer
8	IIIB	PR	12/2	CR		PD (3)	Alive, metastatic disease
9	IIA	PR	25/5	CR			Alive, no disease

CR: Complete response; EBRT: external beam radiation therapy; FU: follow-up; LC: local control; MFS: metastasis-free survival; MRI: magnetic resonance imaging; PD: progressive disease; PR: partial response; SBRT: stereotactic body radiation therapy.

Discussion

Endo/interstitial BT is recommended as a definitive treatment for cervical cancer, as it can deliver high-dose radiation to the tumor while limiting the irradiation of adjacent organs. A population-based analysis revealed that BT use is independently associated with a significantly higher OS, whilst patients unfit for BT are at higher risk of local recurrence (1, 3, 9, 34).

In daily clinical practice, however, perform EBRT alone in patients for whom BT is not possible is sometimes unavoidable, although it is well known that international guidelines suggest an EBRT boost instead of BT boost as a weak recommendation (10, 14).

In our clinical study, on a limited but homogeneous population of nine patients diagnosed with cervical cancer, EBRT boost showed a good profile of efficacy, safety and tolerability in terms of acute and late toxicities. In fact, no severe grade 4 acute or late toxicities were observed during the treatment and only one grade 3 toxicity was reported.

Moreover, a radiological complete response was recorded for all patients at 3 months after SBRT boost, confirming the high rate of local control, while only one cervical recurrence and two metastatic progressions occurred during a median follow-up of 16 months, data which are similar with other data recently published in other series (15, 16, 19, 25). In particular, in our series of patients, local recurrence and progression of metastatic disease were observed in patients with advanced stages of disease (IIIB-IVA) who had gross residual tumor after EBRT and before the SBRT boost.

Since our study was based on very few patients, we can only speculate that residual tumor after EBRT may be related

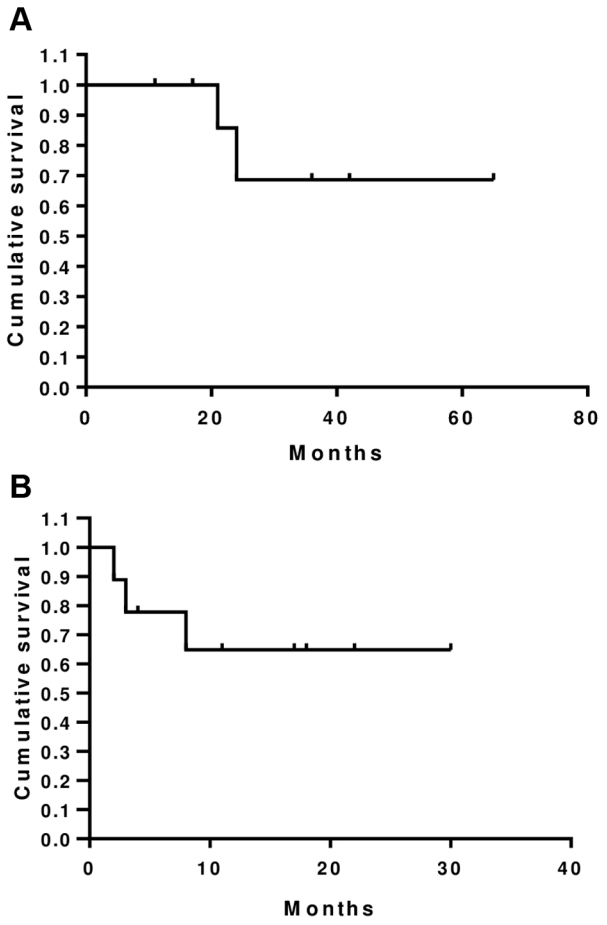

Figure 2. *Overall (A) and disease-free (B) survival considering all nine patients.*

to poor survival outcomes, suggesting that such patients may benefit from a different radiotherapy approach (*e.g.*, proton beam radiation therapy) (35). Nevertheless, among the other patients who achieved complete response after EBRT, no local recurrence or metastatic progression was reported after SBRT boost.

To the best of our knowledge, this is the first clinical study which analyzed the association between gross residual disease after EBRT and SBRT boost dose/fractionations, local control and survival outcomes.

Over the past decade, very few studies evaluated the role of EBRT instead of BT boost. Due to old EBRT techniques delivering a suboptimal dose, and limited and different population studies, the results were almost disappointing (11-13).

Better results were obtained when EBRT was administered as concomitant boost in 10 patients treated with a median dose of 66 Gy with a median overall treatment time of 40 days and 3-year local control rate of 90.0% (34).

The use of IMRT boost treatment in terms of dosimetric and radiobiological parameters may represent a valid alternative approach when BT is not feasible, providing 3-year OS and local control of 93% and 80%, as simultaneous integrated boost (66 Gy as total radiation dose to the tumor; 2.2 Gy/fraction respectively) or 2-year OS, progression-free survival, and local control rate of 67%, 55%, and 78% as sequential boost (25 Gy/5 fractions) (18, 26, 36).

Although both IMRT and SBRT can be delivered using the same accelerator techniques, SBRT is distinguished from IMRT by being able to deliver a high dose per fraction (usually exceeding 5 Gy) and provides accurate sparing of OARs, as in our series.

In a large study of a National Cancer Data Base of locally advanced cervical comparing 42 patients treated with SBRT boost (median dose of 25 Gy/5 fractions), 1,468 who received IMRT boost (median dose 18 Gy/10 fractions) and 1,4394 patients who received BT boost, no significant difference was found in OS between those who received SBRT boost and those who received a BT boost. Patients who received IMRT boost had worse OS when compared with those treated with BT and SBRT boost (17).

There are very limited clinical data in the literature on image-guided SBRT for primary or recurrent gynecological cancer as adjuvant or curative treatment, reporting high rates of local control and low incidence of acute and late toxicities (Table IV) (15-17, 19-22, 25).

The most commonly used SBRT schedules are 20-25 Gy/4-5 fractions or 14-21 Gy/2-3 fractions, delivering the maximum possible dose to the tumor respecting OAR dose constrains, and taking into account EBRT doses previously delivered.

Our institutional daily clinical practice for locally advanced cervical cancer includes IMRT-SIB (66 Gy as total radiation dose to the tumor; 2.2 Gy/fraction respectively) followed by intracavitary BT boost. We maintain the same policy when performing SBRT boost instead of BT boost. This approach of using IMRT as concomitant and SBRT boost may explain the high local control recorded in our series of patients.

Despite the limited number of patients and the heterogeneity of cases among analyzed SBRT studies, the survival outcomes in our series of patients are consistent with the published literature, showing acceptable local control, DFS and OS, especially for patients achieving complete radiological response after EBRT.

In patients with cervical cancer undergoing concurrent chemoradiotherapy and consolidative intracavitary BT, the total treatment time is strongly suggested to be 8 weeks or less in order to maximize pelvic control (37). The total treatment time of our study was 92 days (range=62-104 days), similarly to other studies, due to an unpredictable shift to SBRT boost for patients who refuse brachytherapy or who have cervical stenosis onset.

Table IV. *Published series on patients with cervical cancer treated with stereotactic body radiation therapy boost.*

Author (ref)	Median age (range), years	Patients, n	Median FU (range), months	FIGO stage, n	Dose, Gy	Fractions	LR, n	DM, n	Survival/ LC	Acute toxicity, n	Late toxicity, n
Jorcano *et al*. (16)	62 (37-74)	26	47 (4-77)	I: 17 II: 7 III: 2	7	2	2	1	3-Year FFS: 96% OS: 95%	Dyspareunia: 1 Synechiae: 1 Dryness: 4	Vaginal: dryness: 5 Synechiae: 3 Stenosis: 1
Ito *et al*. (25)	55 (49-74)	6	17 (8-32)	NA	19.5/21/ 22.5	3	1	1	NA	Acute diarrhea 1 Radiation dermatitis 2	Lower limb edema: 1 Vertebral: compression: 1
Mollà *et al*. (19)	53 (33-71)	16	12.6 (6-26)	I: 9 II: 6 III: 1	14/20	2/5	NA	NA	NA	Dyspareunia: 1 Synechiae: 1 Dryness: 3 Pruritus: 1	Vaginal: dryness: 5 Synechiae: 1 Rectal: bleeding: 1
Lazzari *et al*. (18)	55 (30-82)	25	26 (4-77)	IIB: 3 IIIB: 3 IIIC1: 9 IIIC2: 2 IVA: 2 IVB: 6	25	5	5	8	2-Year OS: 67% LC: 78% PFS: 55%	G1-2 Diarrhea/ cystitis: 10	G1-2 Rectal bleeding/proctitis: 8
Kubicek *et al*. (15)	62 (47-81)	11	14 (NR)	NA	25 (15-27.5)*	3-5	2	0	NA	G2 GU/GI: 2	G3 GI bleeding 1
Hsieh *et al*. (20)	68 (46-93)	9	NA	IIB: 4 IIIB: 3 IVA: 2	27 (27-16)	5-9	2	4	3-Year OS: 25.9% DFS: 77.8% MFS 28.6%	G3: 2	G3: 3 G4: 1 (fistula)
Haas *et al*. (21)	80 (71-94)	6	14 (1-28)	IIB: 4 IV: 1 IVA: 1	19.5/20	3/5	NA	NA	NA	No acute toxicities	No late toxicities
Marnitz *et al*. (22)	NR (32-69)	11	6 (NR)	IIB: 8 IIIB: 2	30	5	0	0	6-Month LC: 100%	Hematological: 4	NA
This study	57 (38-79)	9	16 (6-58)	IIA: 3 IIB: 2 IIIB: 1 IIIC: 1 IVA: 2	18 (15-25)*	3-5	1	2	2-Year OS 70%	G1 Bladder: 2 G1 GI: 1	G1: 2 G2: 1 G3: 1

DFS: Disease-free survival; DM: distant metastasis; FFS: failure-free survival; G: grade; GU: genitourinary; GI: gastrointestinal; LC: local control; LR: local relapse; MFS metastases-free survival; NA: not assessed; NR: not reported; OS: overall survival; PFS: progression-free survival. *Median (range) of total dose.

Finally, the results that can be achieved using SBRT boost can be obtained only if the execution of EBRT boost is based on rigorous multimodality imaging using MRI to better define target volumes, with robust plan optimization to provide accurate sparing of OARs and precise treatment delivery through image-guided radiotherapy techniques.

Conclusion

Despite the limited number of patients investigated in our study, EBRT using SBRT technique in patients with cervical cancer ineligible for BT led to acceptable survival outcomes and particularly a safe toxicity profile.

Although a combination of EBRT and BT boost remains the standard of care for locally advanced cervical cancer, SBRT boost may represent a feasible alternative reserved for women unfit for BT without other treatment options.

Further studies are needed to better evaluate the efficacy of a sequential SBRT boost in this setting of patients, to define the optimal EBRT boost dose and to prospectively collect data concerning toxicities and outcomes, and moreover to investigate other feasible alternative therapeutic approaches.

Conflicts of Interest

The Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Authors' Contributions

G. Facondo, G. Vullo, V. De Sanctis: Made substantial contributions to conception of the study, analyzed the data and drafted the article. M. Valeriani, A.M. Ascolese and M.F. Osti: Made substantial contributions to revising the article critically for important intellectual content, helped to draft the article. D. Anzellini, M. Massaro: Helped to draft and revise the article; All Authors critically revised the article, approved the final version to be published, and agree to be accountable for all aspects of the work.

References

1 Colombo N, Carinelli S, Colombo A, Marini C, Rollo D, Sessa C and ESMO Guidelines Working Group: Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *23(Suppl 7)*: vii27-vii32, 2012. PMID: 22997451. DOI: 10.1093/annonc/mds268

2 Huertas A, Oldrini S, Nesseler JP, Courrech F, Rétif P, Charra-Brunaud C and Peiffert D: FIGO stage IB1 cervical carcinoma: Place and principles of brachytherapy. Cancer Radiother *21(2)*: 155-163, 2017. PMID: 28233697. DOI: 10.1016/j.canrad.2016.09.014

3 Karlsson J, Dreifaldt AC, Mordhorst LB and Sorbe B: Differences in outcome for cervical cancer patients treated with or without brachytherapy. Brachytherapy *16(1)*: 133-140, 2017. PMID: 27836496. DOI: 10.1016/j.brachy.2016.09.011

4 Viswanathan AN, Thomadsen B, American Brachytherapy Society Cervical Cancer Recommendations Committee and American Brachytherapy Society: American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. Brachytherapy *11(1)*: 33-46, 2012. PMID: 22265436. DOI: 10.1016/j.brachy.2011.07.003

5 Miglierini P, Malhaire JP, Goasduff G, Miranda O and Pradier O: Cervix cancer brachytherapy: high dose rate. Cancer Radiother *18(5-6)*: 452-457, 2014. PMID: 25151650. DOI: 10.1016/j.canrad.2014.06.008

6 Albuquerque K, Hrycushko BA, Harkenrider MM, Mayadev J, Klopp A, Beriwal S, Petereit DG, Scanderbeg DJ and Yashar C: Compendium of fractionation choices for gynecologic HDR brachytherapy-An American Brachytherapy Society Task Group Report. Brachytherapy *18(4)*: 429-436, 2019. PMID: 30979631. DOI: 10.1016/j.brachy.2019.02.008

7 Sturdza A, Pötter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, Petric P, Šegedin B, Jurgenliemk-Schulz IM, Nomden C, Gillham C, McArdle O, Van Limbergen E, Janssen H, Hoskin P, Lowe G, Tharavichitkul E, Villafranca E, Mahantshetty U, Georg P, Kirchheiner K, Kirisits C, Tanderup K and Lindegaard JC: Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol *120(3)*: 428-433, 2016. PMID: 27134181. DOI: 10.1016/j.radonc.2016.03.011

8 Tanderup K, Ménard C, Polgar C, Lindegaard JC, Kirisits C and Pötter R: Advancements in brachytherapy. Adv Drug Deliv Rev *109*: 15-25, 2017. PMID: 27637454. DOI: 10.1016/j.addr.2016.09.002

9 Vavassori A, Riva G, Spoto R, Lazzari R, Fodor C, Dicuonzo S, Francia CM, Augugliaro M, Facondo G, Cambria R, Comi S, Cattani F, Botta F, Bagnardi V, Rizzo S, Colombo N, Orecchia R and Jereczek-Fossa BA: High precision radiotherapy including intensity-modulated radiation therapy and pulsed-dose-rate brachytherapy for cervical cancer: a retrospective monoinstitutional study. J Contemp Brachytherapy *11(6)*: 516-526, 2019. PMID: 31969909. DOI: 10.5114/jcb.2019.90478

10 Chuang LT, Temin S, Camacho R, Dueñas-Gonzalez A, Feldman S, Gultekin M, Gupta V, Horton S, Jacob G, Kidd EA, Lishimpi K, Nakisige C, Nam JH, Ngan HYS, Small W, Thomas G and Berek JS: Management and care of women with invasive cervical cancer: American Society of Clinical Oncology resource-stratified clinical practice guideline. J Glob Oncol *2(5)*: 311-340, 2016. PMID: 28717717. DOI: 10.1200/JGO.2016.003954

11 Ito K, Shimizuguchi T and Karasawa K: Clinical outcomes following conventional external beam radiotherapy boost in Japanese patients with cervical cancer who are ineligible for intracavitary brachytherapy. Jpn J Clin Oncol *49(3)*: 270-275, 2019. PMID: 30576504. DOI: 10.1093/jjco/hyy187

12 Delgado D, Figueiredo A, Mendonça V, Jorge M, Abdulrehman M and de Pina MF: Results from chemoradiotherapy for squamous cell cervical cancer with or without intracavitary brachytherapy. J Contemp Brachytherapy *11(5)*: 417-422, 2019. PMID: 31749849. DOI: 10.5114/jcb.2019.88116

13 Barraclough LH, Swindell R, Livsey JE, Hunter RD and Davidson SE: External beam boost for cancer of the cervix uteri when intracavitary therapy cannot be performed. Int J Radiat Oncol Biol Phys *71(3)*: 772-778, 2008. PMID: 18207658. DOI: 10.1016/j.ijrobp.2007.10.066

14 Mahmoud O, Kilic S, Khan AJ, Beriwal S and Small W Jr: External beam techniques to boost cervical cancer when brachytherapy is not an option-theories and applications. Ann Transl Med *5(10)*: 207, 2017. PMID: 28603722. DOI: 10.21037/atm.2017.03.102

15 Kubicek GJ, Xue J, Xu Q, Asbell SO, Hughes L, Kramer N, Youssef A, Chen Y, Aikens J, Saul H, Pahlajani N and LaCouture T: Stereotactic body radiotherapy as an alternative to brachytherapy in gynecologic cancer. Biomed Res Int *2013*: 898953, 2013. PMID: 24000329. DOI: 10.1155/2013/898953

16 Jorcano S, Molla M, Escude L, Sanz S, Hidalgo A, Toscas JI, Linero D and Miralbell R: Hypofractionated extracranial stereotactic radiotherapy boost for gynecologic tumors: a promising alternative to high-dose rate brachytherapy. Technol Cancer Res Treat *9(5)*: 509-514, 2010. PMID: 20815422. DOI: 10.1177/153303461000900509

17 O'Donnell B, Shiao JC, Pezzi TA, Waheed N, Sharma S, Bonnen MD and Ludwig MS: Stereotactic body radiation therapy, intensity-modulated radiation therapy, and brachytherapy boost modalities in invasive cervical cancer: a study of the National Cancer Data Base. Int J Gynecol Cancer *28(3)*: 563-574, 2018. PMID: 29324547. DOI: 10.1097/IGC.0000000000001200

18 Lazzari R, Riva G, Augugliaro M, Vavassori A, Dicuonzo S, Cattani F, Comi S, Colombo N and Jereczek-Fossa BA: Intensity modulated radiation therapy boost in locally-advanced cervical cancer in the absence of brachytherapy. Int J Gynecol Cancer *30(5)*: 607-612, 2020. PMID: 32188626. DOI: 10.1136/ijgc-2019-000735

19 Mollà M, Escude L, Nouet P, Popowski Y, Hidalgo A, Rouzaud M, Linero D and Miralbell R: Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy? Int J Radiat Oncol Biol Phys *62(1)*: 118-124, 2005. PMID: 15850911. DOI: 10.1016/j.ijrobp.2004.09.028

20 Hsieh CH, Tien HJ, Hsiao SM, Wei MC, Wu WY, Sun HD, Wang LY, Hsieh YP, Chen YJ and Shueng PW: Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result. Onco Targets Ther *6*: 59-66, 2013. PMID: 23403975. DOI: 10.2147/OTT.S40370

21 Haas JA, Witten MR, Clancey O, Episcopia K, Accordino D and Chalas E: CyberKnife boost for patients with cervical cancer unable to undergo brachytherapy. Front Oncol *2*: 25, 2012. PMID: 22655266. DOI: 10.3389/fonc.2012.00025

22 Marnitz S, Köhler C, Budach V, Neumann O, Kluge A, Wlodarczyk W, Jahn U, Gebauer B and Kufeld M: Brachytherapy-emulating robotic radiosurgery in patients with cervical carcinoma. Radiat Oncol *8*: 109, 2013. PMID: 23638755. DOI: 10.1186/1748-717X-8-109

23 Kim H, Kim YS, Joo JH, Eom KY, Park W, Kim JH, Lee JH, Kim YS, Lee SH, Ahn K, Kim YB, Lee MY and Chang SK: Tumor boost using external beam radiation in cervical cancer patients unable to receive intracavitary brachytherapy: outcome from a multicenter retrospective study (Korean Radiation Oncology Group 1419). Int J Gynecol Cancer *28(2)*: 371-378, 2018. PMID: 29189448. DOI: 10.1097/IGC.0000000000001155

24 Sethi RA, Jozsef G, Grew D, Marciscano A, Pennell R, Babcock M, McCarthy A, Curtin J and Schiff PB: Is there a role for an external beam boost in cervical cancer radiotherapy? Front Oncol *3*: 3, 2013. PMID: 23386995. DOI: 10.3389/fonc.2013.00003

25 Ito K, Kito S, Nakajima Y, Shimizuguchi T, Ogawa H, Nihei K, Tanaka H, Kino N, Yasugi T and Karasawa K: Determining the recommended dose of stereotactic body radiotherapy boost in patients with cervical cancer who are unsuitable for intracavitary brachytherapy: a phase I dose-escalation study. Jpn J Clin Oncol *49(9)*: 856-861, 2019. PMID: 31112278. DOI: 10.1093/jjco/hyz074

26 Pinzi V, Landoni V, Cattani F, Lazzari R, Jereczek-Fossa BA and Orecchia R: IMRT and brachytherapy comparison in gynaecological cancer treatment: thinking over dosimetry and radiobiology. Ecancermedicalscience *13*: 993, 2019. PMID: 32010217. DOI: 10.3332/ecancer.2019.993

27 Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet *105(2)*: 103-104, 2009. PMID: 19367689. DOI: 10.1016/j.ijgo.2009.02.012

28 Lim K, Small W Jr, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, Mell LK, Mayr N, Viswanathan A, Jhingran A, Erickson B, De los Santos J, Gaffney D, Yashar C, Beriwal S, Wolfson A, Taylor A, Bosch W, El Naqa I, Fyles A and Gyn IMRT Consortium: Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys *79(2)*: 348-355, 2011. PMID: 20472347. DOI: 10.1016/j.ijrobp.2009.10.075

29 Tharavichitkul E, Wanwilairat S, Chakrabandhu S, Klunklin P, Onchan W, Tippanya D, Nopnop W, Galalae R and Chitapanarux I: Image-guided brachytherapy (IGBT) combined with whole pelvic intensity-modulated radiotherapy (WP-IMRT) for locally advanced cervical cancer: a prospective study from Chiang Mai University Hospital, Thailand. J Contemp Brachytherapy *5(1)*: 10-16, 2013. PMID: 23634150. DOI: 10.5114/jcb.2013.34338

30 Report 89. J ICRU 13(1-2): NP, 2013. PMID: 27335498. DOI: 10.1093/jicru/ndw042

31 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31(5)*: 1341-1346, 1995. PMID: 7713792. DOI: 10.1016/0360-3016(95)00060-C

32 Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot JC, Bolla M and Bartelink H: EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. Radiother Oncol *35(1)*: 11-15, 1995. PMID: 7569011. DOI: 10.1016/0167-8140(95)97448-m

33 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

34 Matsuura K, Okabe T, Fujita K, Tanimoto H, Akagi Y and Kagemoto M: Clinical results of external beam radiotherapy alone with a concomitant boost program or with conventional fractionation for cervical cancer patients who did not receive intracavitary brachytherapy. J Radiat Res *53(6)*: 900-905, 2012. PMID: 22859563. DOI: 10.1093/jrr/rrs051

35 Kagei K, Tokuuye K, Okumura T, Ohara K, Shioyama Y, Sugahara S and Akine Y: Long-term results of proton beam therapy for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys *55(5)*: 1265-1271, 2003. PMID: 12654436. DOI: 10.1016/s0360-3016(02)04075-0

36 Mazzola R, Ricchetti F, Fiorentino A, Levra NG, Fersino S, Di Paola G, Ruggieri R and Alongi F: Weekly cisplatin and volumetric-modulated arc therapy with simultaneous integrated boost for radical treatment of advanced cervical cancer in elderly patients: feasibility and clinical preliminary results. Technol Cancer Res Treat *16(3)*: 310-315, 2017. PMID: 27402633. DOI: 10.1177/1533034616655055

37 Song S, Rudra S, Hasselle MD, Dorn PL, Mell LK, Mundt AJ, Yamada SD, Lee NK and Hasan Y: The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer *119(2)*: 325-331, 2013. PMID: 22806897. DOI: 10.1002/cncr.27652

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