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Impact of Brachytherapy in the Treatment of Locally Advanced Cervical Cancer: Results from a Single Institution

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Abstract

Introduction: In Morocco, cervical cancer is the second most common cancer, and proximally half of the cases are diagnosed at an advanced stage. The standard treatment approach is concurrent chemoradiation followed by intracavitary brachytherapy (BT) boost to the cervix.

Patients and methods: 293 patients diagnosed with cervical cancer and treated with concurrent chemoradiotherapy between January 2011 and December 2011 at our department was retrieved. We analyzed defined prognostic factors influencing outcomes. The aim of our study is to analyze the effect of the use of brachytherapy on treatment outcomes (overall survival and local control) and to report the toxicities for each treatment approach.

Results: At 3 years, the use of brachytherapy as boost was found to be a significant factor impacting both OS (P=0.0001)), and LC (P=0.001). Also in the multivariate analysis, brachytherapy was an independent prognosis factor affecting both OS (hazard ratio [HR], 3.29; 95% CI, 1.50-7.21, P=0.03) and LC (hazard ratio [HR], 2.33; 95% CI, 1.30-7.21, P=0.005).

Conclusion: At present, brachytherapy is still the standard approach to boost the cervix in patients with locally advanced cervical cancer.

Keywords: Cervical cancer; Concurrent chemoradiotherapy; Brachytherapy; Treatment duration; Prognosis factors

Abbreviations: BT: Brachytherapy; FIGO: Federation of Gynecology and Obstetrics; OS: Overall Survival; LC: Local Control; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EBRT: External Beam Radiation; LACC: Locally Advanced Cervical Cancer; LDR: Low Dose Rate; HDR: High Dose Rate; SBRT: Stereotactic Body Radiation Therapy; IMRT: Intensity Modulated Radiation Therapy; Ci: Curie; IGABT: Image Guided Adaptive Brachytherapy

Introduction

In Morocco, cervical cancer is the second most common cancer, and is the third most common cause of death in women [1]. Our department recruits more than 500 patients each year and is diagnosed at an advanced stage in more than half of the cases. Local control is particularly compromised in this population.

After the National Cancer Institute Alert in 1999 [2], showing a 30-50% decrease in risk of death. Chemotherapy concomitantly with radiation has become the standard of care in women with cervical cancer. Radiation treatment is typically external beam radiation therapy to the pelvis followed by intracavitary brachytherapy (BT) boost to the cervix.

Brachytherapy (BT) plays an essential role in the treatment of patients with locally advanced cervical cancer. Han et al. reported recently a decline in utilization of brachytherapy in some centers in the United States that was associated with 15% decrease in overall survival [3].

However, because of the tumor bulk and/or anatomical distortion, some patients with locally advanced cervical cancer could not be suitable for intracavitary brachytherapy after receiving EBRT to pelvis. The boost can be delivered to the tumor using conventional EBRT or IMRT instead of brachytherapy.

Materials and Methods

Patients

All women treated for invasive cervical cancer in our institute between January 2011 and December 2011 was identified. Our study included only women patients treated with primary chemo radiotherapy and that were able to complete the total dose of radiotherapy (either by brachytherapy or external beam radiotherapy).

Of the 325 patients selected, 32 patients were excluded as they did not complete the planned treatment (all of those patients stopped their treatment without the institutions' consent and we were not able to make contact with them).

At total of 293 patients treated with concomitant chemoradiotherapy were included in the study.

For each patient, the following data were collected for analysis of the prognostic factors: age, histologic type, tumor size, stage, presence of lymphadenopathy, pretreatment hemoglobin level, mean hemoglobin during treatment, number of cycles of chemotherapy, external beam RT dose, brachytherapy when given, and overall treatment duration.

The aims of our study are to analyze the effect of the use of brachytherapy on treatment outcomes (overall survival and local control) and to report the toxicities of each treatment approach.

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Treatment Modalities

Concurrent chemo radiotherapy with weekly cisplatin in combination with brachytherapy is the standard treatment adopted in our department.

External beam radiotherapy (EBRT) technique

EBRT was delivered using linear accelerators from ELEKTA with High-energy photon beams 18 MV. In the first phase, a total dose of 46 Gy was given to pelvis either by antero posterior fields or box technique using four fields (Anterior-posterior (2/3 of dose) and two laterals (1/3 of dose)). Also, for a maximal sparing of the bowel and bladder and normal bone structures, a conformal blocking was used in all the cases.

Clinical target volume included the gross disease, corpus, parametria with a vaginal margin of 3 cm from the gross disease. The nodal target volume for patients with negative nodes on radiologic imaging included the entirety of the external iliac, internal iliac, and obturator nodal basins. The radiation volume was increased to cover the common iliac as well for patients with suspected or confirmed nodes confined to the low true pelvis.

Once the first phase achieved, the evaluation of the tumor response and the feasibility of brachytherapy was made by both clinical examination and CT scan when available.

When brachytherapy was not feasible, the second phase consisted on a boost of 24 Gy to the whole cervix with margin of 2 cm. Treatment was also delivered using box technique.

At the end of brachytherapy, an additional dose of 10 Gy in five fractions was delivred as boost to parameters when involved. Also, an additional dose of 14 to 20 Gy was systematically delivered to any proven positive lymph nodes.

Chemotherapy

Concurrent chemotherapy with cisplatin has been given at our center since 2001. A dose of 40 mg/m2 with a maximum of 70 mg is given weekly throughout the course of RT as long as the treatment is tolerated.

In case of renal failure, carboplatine (air under the curve 2) was prescribed (13% of the cases).

Brachytherapy

Patients were treated either by Low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy.

Iridium Ir192 (10 Curie (Ci)) was used as source in HDR brachytherapy, and Ir192 IRF2 (10 mCi/cm) in LDR brachytherapy.

Treatment was delivered using manual loading when we opted for LDR brachytherapy; applicators used in this case were the colpostat of Delouche (one intra uterine tube and 2 vaginal tubes with ovoids (3 different sizes)). In HDR brachytherapy, treatment was performed using microselectron HDR from Nucletron with CT/MR compatible applicators: Fletcher or ring applicators.

Application Modalities

Applicators placement was performed under epidural anesthesia in all the cases. A foley catheter was placed in the bladder. A speculum was then placed to visualize the cervix. The ovoids or ring were placed after the insertion of the tandem. Once the applicator in place, it was stabilized by gauze packing. Then, when the posterior wall was not involved, the rectum was displaced away from the applicator by using an in-built rectal retractor, also, the bladder was displaced using an anterior vaginal packing when the anterior wall was not involved.

After implantation, a simulation was performed using a CT scan and a 3D treatment was carried out. Otherwise, two orthogonal X-rays were taken, and a standard two-dimensional (2D) treatment planning was performed.

Dosimetry

Following the completion of applicator insertion, patients underwent X-Rays or CT scan. In both cases, dummy source catheters were inserted into the tubes of the applicator to help the reconstruction of the applicator. The images were then transferred onto Nucletron plato.

For LDR brachytherapy, the reference isodose was choosing depending of the size of the residual tumor and then the treatment duration was calculated, the prescribed dose was 24 Gy.

For HDR brachytherapy, the two-dimensional (2D) treatment planning was based on a standard loading pattern. In cases of three dimensional planning, once CT scan realized, the delineation of high risk, intermediate risk clinical target volumes and organs at risk (bladder, rectum and sigmoid), was made following the guidelines of the Groupe Européen de Curiethérapie –European Society of Radiation Oncology (GEC–ESTRO). A systematic prescription of 4×7 Gy was normalized to points A.

Follow-up

Patients were followed up for 3 years by radiation oncologists. Relapse was documented by positive biopsy, clinical examination (examination under anesthesia whenever it was needed), or radiographic results.

The median follow up was 31 months (Range [18-44 months]).

Statistical analysis

The Kaplan-Meier method was used to analyze OS and LC. Univariate analysis was performed using the log–rank test. Multivariate analysis was performed using the Cox proportional hazards model hazard regression analysis in a forward stepwise manner with a P value of 0.2 as inclusion. Statistical analysis was performed with SPSS software. A value of $P<0.05$ was considered statistically significant.

Results

Clinico-pathologic characteristics

Mean age for the whole group of patients in this study was 51 (range 26–78 years).

The predominant histologic type was squamous cell carcinoma (94.9% of the cases) (n=278).

Tumor size was superior to 4 cm in 54.6%, and parametrial involvement was recorded in 83%.

All the patients were staged according to the FIGO staging system of 2009, 9.5 % of the patients were staged as IB, and stages IIA, IIB, IIIA, IIIB , IVA were found in 4.4%, 44.4%, 0.7%, 38.6% and 1.7% of the cases (Tables 1 and 2).

Treatment modalities

Twenty nine percent of patients were treated by EBRT alone without brachytherapy (70 Gy).

	N	%
Age (y)	**50 [44–59]**	
Histologic Type		
Squamous cell carcinoma	278	94,9 %
Adenocarcinoma	15	5,1 %
Revealing symptom		
Metrorrhagia	231	79%
Leucorrhea	205	70%
Pelvic pain	131	45%
Tumor size		
<4 cm	133	45.40%
>4 cm	160	54.60%
Stages		
IB	28	9.50%
IIA	13	4.40%
IIB	131	44.40%
IIIA	2	0.70%
IIIB	114	38.60%
IVA	5	1.70%

Table 1: Clinicopathologic characteristics of the studied patients.

	N	%
Lymphadenopathy		
Pelvien	66	22.50%
Para aortic	11	3.8
Distance metastasis	0	0%
Pretreatment hemoglobin level		
<10 g/dL	60	20.30%
10-11.9 g/dL	103	34.90%
≥12	130	44.10%

Table 2: Radiological and biological characteristics of the studied patients.

The median overall treatment time was 61 days (53-71 days) and was beyond 56 days in 61.7%. The median duration of the first phase of external radiotherapy (delivering a total dose of 46 Gy) was 37 days (34-42 days) (Table 3).

The median duration between the end of radiotherapy (46 Gy) and the beginning of brachytherapy was 15 days (10-23 days).

46% of patient received additional boost on the parameters and/or the lymph nodes at the end of brachytherapy (after 7 days).

Brachytherapy was performed in 71% of the cases, Of the 208 patients who received brachytherapy, LDR brachytherapy was used in 73.6% of the cases, and HDR brachytherapy in the remaining 26.4% with four fractions of 7 Gy (one fraction per week). Only intracavitary approach was used. Applicator was chosen depending on the patient anatomy and tumor characteristics. We used tandem and ovoids in 38% of the cases and ring applicator (when the vaginal fornices were asymmetric or absent) in 19% of the cases.

The rectum and bladder was displaced away from the applicator respectively in 28% and 32% of the cases.

After implantation of the applicators, two orthogonal X-rays were taken, and standard 2D treatment planning was performed in 95.7% of the cases, and pelvic CT for control was realized in 4.3% of the cases.

Reasons for being unable to perform brachytherapy was dominate by the inability to cannulate the cervical os, which was obstructed by residual tumor or had disintegrated, leaving a large hole.

Also, because of the absence of interstitial catheters in our department, we were unable to perform brachytherapy when the uterus (8% of the cases) or the lower vagina with a thickness of more than 5 mm (18% of the cases) was involved.

Of the five planned cycles of concurrent cisplatin chemotherapy, 243 patients (82.4%) received four or more cycles. The main reason for patients having reduced number of cycles was acute hematologic toxicity.

Treatment toxicities

Toxicities were graded according to common terminology criteria of adverse events (CTCAE).

Acute toxicities: All patients had a weekly evaluation along with a blood cell account and a dosage of urea and creatinine levels. Only 74% patients were closely monitored. We could not find any data concerning the remaining patients (Table 4).

The most common acute adverse effects were gastrointestinal and renal insufficiency.

Patients who had brachytherapy as boost reported less toxicities than who received EBRT boost (grade 3 or 4 gastrointestinal toxicities were noted in 9.2% of patients who received brachytherapy as boost while it was reported for 19.2% of patients who received only EBRT. The same continuation was found for hematologic and renal toxicities).

Late toxicities: Late complications were defined as occurring more than 3 months after the first day of radiotherapy. Late grade 3 or 4 complications were noted in 52 cases. The late toxicities experienced by these women are summarized in Table 5.

	N	%
EBRT alone without Brachytherapy	85	29%
Brachytherapy		
LDR	153	73.60%
HDR	55	26.40%
Implantation control		
2D	198	95.1
CT	10	4.9

Table 3: Treatment modalities.

	EBRT +Brachytherapy boost		EBRT alone	
N=293	**N (208)**	**%**	**N (85)**	**%**
Gastrointestinal				
Grade 1 or 2	70	7.7	35	11.5
Grade 3 or 4	30	9.6	31	19.2
Hematologic toxicities				
Neutropenia				
Grade 1 or 2	5	2.4	3	3.5
Grade 3 or 4	10	4.8	10	11.7
Anemia				
Grade 1 or 2	80	38.4	37	43.5
Grade 3 or 4	4	1.9	5	5.8
Thrombopenia				
Grade 1 or 2	1	0.4	1	1.17
Grade 3 or 4	1	0.4	2	2.3
Renal insufficiency				
Grade 1 or 2	51	24.5	30	35.2
Grade 3 or 4	11	5.2	22	25.8

Table 4: Treatment-related acute toxicities.

	EBRT +Brachytherapy boost		EBRT alone	
N=52	**N**	**%**	**N**	**%**
Gastrointestinal				
Grade 1 or 2	4	7.7	6	11.5
Grade 3 or 4	5	9.6	10	19.2
Genitourinary				
Grade 1 or 2	3	5.7	3	5.7
Grade 3 or 4	1	1.9	4	7.7
Thromboembolic				
Grade 1 or 2	1	1.9	3	5.7
Grade 3 or 4	1	1.9	3	5.7
Renal				
Grade 1 or 2	5	9.6	12	23
Grade 3 or 4	6	11.5	10	19.2

Table 5: Treatment-related late toxicities.

Of these 52 patients, 32 patients with severe late toxicity were treated to full-dose EBRT without brachytherapy.

OS and LC

The overall 3-year survival rate was 89.8%, and the overall LC rate was 80.8% at 3 years.

Univariate analysis

The univariate analysis examined prognosis factors affecting the aforementioned variables. The use of brachytherapy as a component in the treatment was found to be a significant factor influencing both OS (p=0.0001) (Figure 1) and LC (p=0.001) (Figure 2) (Tables 6 and 7).

Also OS and LC was significantly affected by tumor size, the presence of positive lymph nodes, pretreatment hemoglobin, the total treatment duration (>56 days), and the number of cycles of chemotherapy completed (less than four).

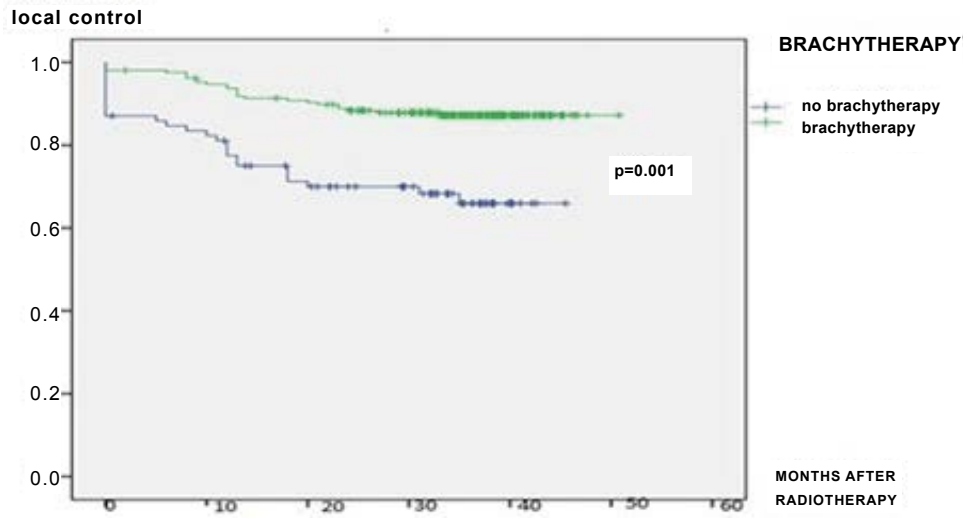

Figure 1: Graph showing the impact of brachytherapy on overall survival.

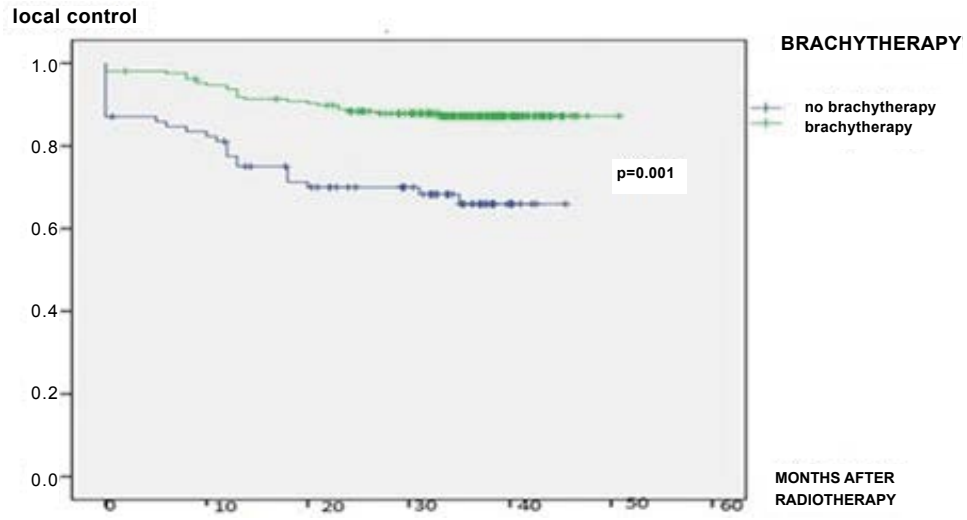

Figure 2: Graph showing the impact of brachytherapy on local control.

		Univariate analysis	Multivariate analysis		
	%	p	p	HR	IC 95%
Age					
≤49	44.40%	0.56	Not included		
>49	55.60%				
Histologic type					
Squamous cell carcinoma	94.90%	0.89	Not included		
Adenocarcinome	5.10%				
Size					
≤4 cm	45.40%	0.003	0.75 (NS)	1.18	0.40-3.46
>4 cm	54.60%				
Lymphadenopathy					
No	76.70%	0.0001	0.08	1.9	0.91-4.14
Yes	23.10%				
Stage					
Local	58.30%	0.0001	0.028	2.79	1.11-6.97
Locally advanced	41.70%				
Pretreatment hemoglobin level					
<10 g/Dl	20.30%	0.004	0.47(NS)	1.43	0.53-3.83
10-11.9 g/dL	34.90%				
≥12 g/dL	44.10%				
Number of cycle Of chemotherapy		0.028	0.059	2.15	0.97-4.76
<4	16.90%				
≥4	82.40%				
Treatment duration					
≤56 days	38.30%	0.014	0.035	2.84	1.07-7.54
>56 days	61.70%				
Brachytherapy					
No	29%	0.0001	0.03	3.29	1.50-7.21
Yes	71%				

Table 6: Uni and multivariate analysis for prognosis factors influencing OS.

Multivariate analysis

With the use of the Cox regression model, brachytherapy was associated independently with prognosis, and affected both OS (hazard ratio [HR], 3.29; 95% CI: 1.50-7.21, p=0.03) and LC (hazard ratio [HR], 2.33; 95% CI:1.30-7.21, p=0.005) (Tables 6 and 7).

The others independently significant variables identified for both the LC and OS were the total treatment duration (>56 days), the stage and number of cycles of chemotherapy completed (less than four).

Discussion

Concurrent chemoradiation plus intracavitary brachytherapy is considered to be the standard approach for locally advanced cervical cancer [3,4].

Since the results of many randomized trials, and the National Cancer Institute alert in 1999, showing that the addition of chemotherapy to radiotherapy improves patient outcomes [5]. Concurrent chemotherapy to radiation has been introduced as standard of care in women with advanced cervical cancer.

Many studies have associated the use of brachytherapy with improved patient control and enhancing survival [6-11]. Multiple reports, including patterns of care studies, have shown that BT used as boost after EBRT significantly improves survival and that local control is highly dependent on the dose delivered by the intracavitary sources through BT [12-16].

In a recent report by Han et al. [17], brachytherapy treatment was associated with higher 4-year cause-specific survival (CSS; 64.3% vs 51.5%, P<.001) and overall survival (OS; 58.2% vs 46.2%, p<.001). Brachytherapy was independently associated with better CSS (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.57-0.71), and OS (HR 0.66; 95% CI, 0.60 to 0.74).

More recently, with the development of image-guided adaptive BT (IGABT), a modern technique allowed by the possibility to integrate 3D images in treatment planning. IGABT allows dose escalation to the tumor while controlling the dose delivered to organs at risk. Preliminary studies showed high local control rates, even in advanced stages [18] and distant metastases became, by far, the first site of recurrence [19]. A dose-effect relationship in patients treated with high dose rate image guided BT was demonstrated by Dimoupoulos et al. [20].

However, because of the tumor bulk and/or anatomical distortion, some patients with locally advanced cervical cancer could not be suitable for intracavitary brachytherapy after receiving EBRT to pelvis. The boost can be delivered to the tumor using conventional EBRT or IMRT instead of brachytherapy.

	Univariate analysis	Multivariate analysis		
%	p	p	HR	IC 95%
Age				
≤49 44.4 %	0.2	Not included		
>49 55.6%				
Histologic type				
Squamous cell carcinoma 94.9 %	0.886	Not included		
Adenocarcinome 5.1%				
Size				
≤4 cm 45.4%	0.005	0.63 (NS)	1.18	0.59-2.36
>4 cm 54.6%				
Lymphadenopathy				
No 76.7%	0.017	0.98	0.99	0.52-1.87
Yes 23.1%				
Stage				
Local 58.3%	0.002	0.008	2.3	1.24- 4.28
Locally advanced 41.7%				
Pretreatment hemoglobin level				
<10 g/Dl 20.3%	0.033			
10-11.9 g/dL 34.9%		0.99 (NS)	0.99	0.51-1.94
≥12 g/dL 44.1%				
Number of cycle of chemotherapy	0.025	0.056	1.82	0.98-3.37
<4 16.9%				
≥4 82.4 %				
Treatment duration				
≤56 days 38.3 %	0.0001	0.001	3.23	1.57-6.64
>56 days 61.7 %				
Brachytherapy				
No 29%	0.001	0.005	2.33	1.30-7.21
Yes 71%				

Table 7: Uni and multivariate analysis for prognosis factors influencing LC.

Actually, with the advent of advanced EBRT techniques, such as stereotactic body radiation therapy (SBRT) or intensity-modulated radiation therapy (IMRT) techniques. Many studies reported the decline of the use of BT to boost the cervix in women with cervical carcinoma [17,21]. This trend is also reported in other gynecologic cancers, such as the vaginal cancer [22].

In a report who analyzed the boost treatment in patients with Stage IIB e IVA cervical cancer treated from January 2004 to December 2011. Gill, et al. showed a decline of the use BT from 97% to 86% between 2004 and 2011, whereas IMRT or SBRT use concomitantly increased from 3.3% to 13.9%. It also showed that IMRT or SBRT boost resulted in inferior overall survival (hazard ratio 0.65, 95% confidence interval, P<.01) as compared with BT. Interestingly enough, omission of brachytherapy was associated with a survival detriment stronger than that associated with excluding chemotherapy [21].

Contrary to brachytherapy, the use of IMRT or SBRT entails more low-dose radiation to surrounding normal tissues, with an increased risk of secondary malignancies as compared with BT especially in younger patients with cervical carcinoma.

In this study, the use of brachytherapy was associated with better local control and overall survival. Also higher toxicities were observed when radiotherapy was performed without brachytherapy; in fact those patients underwent more chemotherapy cycles and received a higher dose of EBRT to adjacent organs which may explain the increase of toxicities.

However, as for most retrospective series, our study has some limitations. Toxicity evaluation was likely to be underestimated, also because of the relatively short follow-up period that was 3 years, longer follow up is necessary to draw conclusions. Another criticism to our study was that radiotherapy boost was not optimal delivered with box technique, comparison between IMRT and BT would be more interesting.

Conclusion

The use of brachytherapy in combination with EBRT was found as an independent prognostic factor, affecting both OS and LC. At present, it would be inappropriate to routinely replace BT with any of the EBRT techniques to boost the cervix in patients with locally advanced cervical cancer who have no contraindications to BT.

We recognize, however, that for patients whose anatomy precludes BT use, or refuse BT, a conformal EBRT boost using IMRT may be a reasonable alternative.

Conflict of Interest

We declare not having any conflict of interest.

Informed Consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' Contributions

NS; HB; SB and JK contributed in the analysis of patient's charts, in the literature review and in writing the manuscript. HE and SE corrected the manuscript before submission. TK and NB participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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