

The impact of different treatment protocols on achieved radiation doses of high-dose-rate brachytherapy for locally advanced cervical cancer: a comparison between 2 fractions in 1 application and separate applications for each fraction

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Abstract

Purpose: To compare radiation doses achieved by image-guided brachytherapy for locally advanced cervical carcinoma implemented with two different protocols.

Material and methods: Medical records of 117 patients with locally advanced cervical carcinoma treated with brachytherapy from 2009 to 2018 at our institution were retrospectively reviewed. All patients had received previous external beam radio/chemotherapy. We performed magnetic resonance image-guided adaptive high-dose-rate brachytherapy delivered by intra-cavitary/interstitial applicators. Dose prescription was 7 Gy for four fractions within two weeks. Original schedule of brachytherapy was two fractions delivered on consecutive days with one applicator insertion; this process was repeated one week later (group 1, 54 patients). From 2015 onwards, another protocol of brachytherapy was mainly used, separately performing applicator insertions for each of the four administered fractions (group 2, 63 patients).

Results: The high-risk clinical target volume (HR-CTV) D₉₀ planning aim (PA) of ≥ 85 Gy (hard constraint) was not achieved in 9 cases out of 54 (17%) in group 1 compared with only 2 out of 63 cases (3%) in group 2 ($p = 0.022$). A difference between the two groups was also found in the fulfillment of PA 90 Gy (soft constraint) ($p = 0.027$). We conducted a sub-group analysis of target volume groups and observed that the differences were most pronounced with very large tumors (> 50 cm³). In these patients, PA 85 Gy was only fulfilled in 67% cases when treatment involved two applications, but in all cases with four separate applicator insertions ($p = 0.010$).

Conclusions: In our experience, by performing an applicator insertion for each of the fractions, it is possible to correct the non-optimal position of the applicator immediately, and to deliver better doses for consecutive fractions. As a result, the planning aim is more often achieved, especially for large tumors.

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Purpose

External beam radiotherapy (EBRT) combined with concomitant weekly cisplatin-based chemotherapy and followed by brachytherapy (BT), is the treatment of choice for patients with locally advanced cervical carcinoma (LACC). Brachytherapy improves clinical outcomes and has become the standard of care nowadays. The technique called ‘three-dimensional image-guided adaptive BT’ (IGABT) has evolved over the last 20 years, and today increasingly in the form of magnetic resonance imaging

(MRI)-guided BT. In 2000, the GEC-ESTRO GYN working group was established to develop and unify gynecological IGABT [1-3]. Recommendations for IGABT contouring and dose reporting for LACC have been published by the working group. The group initiated a multicenter prospective study, called ‘International study on MRI-based brachytherapy in cervical cancer’ (EMBRACE-1) in 2008. Based on the results of this study, dose prescription recommendations have been created for primary tumor targets and organs at risk (OARs). This subject has

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been considered by the International Commission on Radiation Units and Measurements (ICRU) Report 89, and published as "Prescribing, recording, and reporting brachytherapy for cancer of the cervix" [4].

While the benefit of BT in definitive radiotherapy of LACC is undeniable, there have been major differences in its' implementation, including low-dose-rate (LDR), high-dose-rate (HDR), and pulsed-dose-rate (PDR) BT. A new possibility with a lower price is electronic brachytherapy, but its' disadvantage is the lack of compatibility with interstitial needles [5]. HDR-BT is the most common modality applied in BT today. Modern HDR-IGABT is a complex medical procedure, which requires resources. HDR-BT for LACC consists of 2-5 fractions, with prescription doses of 3.5-9 Gy [6-9] delivered intracavitarily, and if needed, also with an interstitial component. Treatment protocols with two or more fractions implemented by a single application on consecutive days may save resources. A previous study demonstrated that geometric differences in the applicator position relative to the target and OARs had only a minor overall dosimetric effect, when one applicator insertion was used for the delivery of two HDR fractions within a 16-20-hour time interval [10].

To our knowledge, no studies have been published comparing the effect of brachytherapy implementations (keeping the applicator in situ overnight, or performing an application for each of the fractions), with respect to delivered doses to the target and OARs. Therefore, the aim of this study was to assess the dosimetric effects on (1) the delivered radiotherapy doses, and (2) the clinical and toxicity results as well as (3) the difference in cost, when four BT fractions were performed with two applicator insertions versus four separate insertions for each of the four fractions.

Material and methods

In this retrospective study, we analyzed the data of all LACC patients treated with a curative intent by MRI-based IGABT from January 2009 to December 2018 in Kuopio University Hospital, Finland. Study cohort of 117 patients and treatment protocol have been previously reported in detail [11]. Briefly, all patients had received EBRT, and most of them had also been treated concurrently with chemotherapy. EBRT was immediately followed by MR image-guided HDR brachytherapy, either delivered intracavitarily, or in a combined intra-cavitary and interstitial form. Brachytherapy was performed with four fractions administered over two weeks. The dose for each BT fraction was 7 Gy prescribed to high-risk clinical target volume (HR-CTV). An interstitial ring applicator or advanced gynecological applicator with a possibility of oblique needles (both Elekta™) was utilized, and in some cases, separate free-hand needles, which were not inserted through the applicator's needle holes were used. The first applicator insertion was planned based on T2-weighted diagnostic and control (performed during the last week of chemo/radiotherapy) MRI, and gynecological examination (at the time of diagnosis and at the time of applicator insertion).

Contouring and dose optimization were performed based on MRI, according to ICRU/GEC-ESTRO and EMBRACE recommendations. There were no essential changes in the implementation of treatment during the study period. The plan was optimized using an automatic dose optimization algorithm, and then corrected using graphic and manual optimization (treatment planning system changed from BrachyVision (Varian Medical Systems™) to Oncentra Brachy (Elekta™) in 2016), and standardized loading patterns were not used. Planning aim (PA) of a total dose including EBRT and BT to 90% of HR-CTV (HR-CTV D_{90}), converted into radiobiologically equivalent 2 Gy fractions (using an α/β value of 10 Gy) was preferably 90 Gy, but at least (hard constraint) 85 Gy. For OARs (using an α/β value of 3 Gy), optimization goals (hard constraints) of D_{2cm^3} doses were < 90 Gy for the bladder, and < 75 Gy for the rectum and sigmoid. For the recto-vaginal point, the optimization goal was 75 Gy, but this was not evaluated in this study. The bowel was only systematically contoured in later cases.

Initially, our BT protocol comprised two HDR fractions delivered on consecutive days, with one applicator insertion. MR imaging was performed on the day of applicator insertion, and control computer tomography (CT) was performed on the next day. CT and MR images were fused using applicator geometry. Locations of interstitial needles were verified, and the position was corrected if necessary. For the target volume, we used HR-CTV contoured on the previous day. OARs were always contoured to new images if there had been a motion. Dose distribution was then revised and corrected if necessary. Reporting of the doses to HR-CTV and OARs was based upon the updated results. A similar pattern was repeated on the following week. Since 2015, applicator insertion with MRI and planning has mainly been conducted separately for each of the four fractions. CT imaging has not been used in the planning.

Statistical analyses were performed using IBM SPSS software, version 26. The groups were compared with standard statistical tests. Pearson's chi-square test and Fisher's exact test were applied to evaluate categorical variables, and 2-sided independent samples *t*-test was used for normally distributed continuous variables. Descriptive information was presented as percentages for categorical variables and as means (standard deviations; SD) or medians (ranges) for continuous variables. For statistical significance, an alpha level of 0.05 was considered.

Results

Over a 10-year period, we treated 117 LACC patients with a curative intent with EBRT ± chemotherapy and BT. Our study cohort was treated with two different BT schedules: four fractions completed either in two applicator insertions ($n = 54$, 46.2%, group 1) or with four separate insertions ($n = 63$, 53.8%, group 2). Background characteristics of the patients, tumors, and brachytherapy implementation are presented in Table 1.

The mean delivered dose to HR-CTV D_{90} was 93.7 Gy (SD = 6.1) for the entire group of patients; there were no differences in the mean delivered doses to the target

Table 1. Comparison of the patients, tumors, and implementation of brachytherapy in the two study groups

Variable		Group 1, n = 54	Group 2, n = 63	p-value
Age (years), median (range)		59 (27-88)	51 (31-79)	0.011
FIGO 2009 stage, n pts (%)	I	5 (9.4)	7 (10.9)	0.37
	II	33 (62.3)	45 (70.3)	
	III	10 (18.9)	5 (7.8)	
	IV	5 (9.4)	7 (10.9)	
Tumor maximum width on MRI (cm), mean (SD)		5.7 (1.9)	5.5 (1.6)	0.66
HR-CTV volume (cm ³), mean (SD)		46.8 (25.8)	43.1 (19.3)	0.38
Interstitial needles, n pts (%)	Yes	45 (84.9)	64 (100.0)	0.001
	No	8 (15.1)	0 (0.00)	

volume between the patients treated according to these two BT schedules. The mean HR-CTV D_{90} was 93.0 Gy (SD = 7.4) for group 1, and 94.0 Gy (SD = 5.4) for group 2 ($p = 0.40$). With respect to OARs, the dose ($D_{2\text{cm}^3}$) to the rectum was significantly higher in the group 1 than in the group 2 (67.0 Gy vs. 63.6 Gy, respectively, $p = 0.01$). No differences between the groups were detected in the doses to the bladder or sigmoid (79.8 Gy vs. 80.8 Gy, $p = 0.42$, and 65.8 Gy vs. 67.5 Gy, $p = 0.22$, respectively).

Nevertheless, the fulfillment of both PAs to HR-CTV D_{90} (soft constraint 85 Gy and hard constraint 90 Gy) was less often achieved in the patients treated with two applications than in the patients treated with four applications. The PA of 85 Gy was not achieved in 16.7% of the patients in group 1 compared with only 3.2% in the group 2 ($p = 0.022$). For the PA of 90 Gy, a significant difference was found ($p = 0.027$). However, no significant differences were detected in the cases that exceeded the constraints for OARs (Table 2).

If necessary, the subsequent applicator insertion was amended (the type or size of applicator, or the number or position of interstitial needles was changed) to cover

the target volume better. Alterations of this kind were possible once in the group 1, while in the group 2, there were three opportunities to correct the position of the applicator and needles. The mean delivered doses of HR-CTV D_{90} per fraction and the number of needles per fraction are presented in Table 3.

We divided the patients into three groups according to the HR-CTV volume (small tumors: $\leq 30 \text{ cm}^3$, medium-sized tumors: $30.1\text{-}50 \text{ cm}^3$, and large tumors: $> 50 \text{ cm}^3$), and performed a sub-group analysis. Table 4 presents the dose volume parameters and fulfillment of PAs of 85 Gy and 90 Gy for HR-CTV D_{90} for the volume sub-groups. In the groups of small and medium tumors, there was no difference between different application protocols, but a significant difference was detected with tumors larger than 50 cm^3 . With the largest tumors treated in the group 1, the PAs of 85 Gy and 90 Gy were less often achieved than in the group 2 ($p = 0.010$ and $p = 0.043$, respectively). In addition, the HR-CTV D_{90} mean dose was significantly better in the group 2 ($p = 0.09$). The two different treatment protocols had no effect on the doses delivered to OARs in the three volume sub-groups.

Table 2. Fulfillment of the planning aims for target volumes and keeping delivered doses to organs at risk under pre-defined targets

Volumes and doses	Group 1, n = 54 n (%)	Group 2, n = 63 n (%)	p-value
HR-CTV D_{90} (≥ 85 Gy)	45 (83.3)	61 (96.8)	0.022
HR-CTV D_{90} (≥ 90 Gy)	36 (66.7)	53 (84.1)	0.027
$D_{2\text{cm}^3}$ bladder (< 90 Gy)	51 (94.4)	61 (96.8)	0.660
$D_{2\text{cm}^3}$ rectum (< 75 Gy)	45 (83.3)	59 (93.7)	0.087
$D_{2\text{cm}^3}$ sigmoid (< 75 Gy)	50 (92.6)	53 (84.1)	0.250

HR-CTV D_{90} – minimum dose to 90% of high-risk clinical target volume, $D_{2\text{cm}^3}$ – minimum dose to maximally irradiated 2 cm^3

Table 3. HR-CTV D_{90} delivered doses and number of interstitial needles used per fraction, fractions 1 to 4

Fraction	Group 1, n = 54		Group 2, n = 63	
	HR-CTV D_{90} dose (Gy), mean (SD)	Number of needles, mean (SD)	HR-CTV D_{90} dose (Gy), mean (SD)	Number of needles, mean (SD)
Fraction 1	7.7 (1.2)	3.5 (2.3)	7.6 (1.2)	4.8 (2.6)
Fraction 2	7.6 (1.1)	3.5 (2.3)	7.9 (0.8)	5.6 (2.7)
Fraction 3	7.9 (1.0)	3.9 (2.5)	8.1 (0.5)	5.8 (2.6)
Fraction 4	7.8 (1.0)	3.9 (2.5)	8.0 (0.6)	5.8 (2.5)

HR-CTV D_{90} – minimum dose to 90% of high-risk clinical target volume

Table 4. HR-CTV D₉₀ doses and fulfillment of the planning aims of 85 Gy (hard constraint) and 90 Gy (soft constraint) in different target volume groups

Volume groups	n	HR-CTV D ₉₀ mean dose (SD)			Fulfilled PA 85 Gy			Fulfilled PA 90 Gy		
		Group 1	Group 2	p-value	Group 1	Group 2	p-value	Group 1	Group 2	p-value
Vol. ≤ 30 cm ³	30	97.5 (6.1)	95.9 (6.2)	0.50	91.7%	94.4%	1.00	91.7%	83.3%	0.63
Vol. 30.1-50 cm ³	48	93.6 (5.4)	93.8 (4.2)	0.88	95.2%	96.3%	1.00	71.4%	85.2%	0.30
Vol. > 50 cm ³	39	89.8 (8.5)	93.4 (3.7)	0.09	66.7%	100.0%	0.010	47.6%	83.3%	0.043

HR-CTV D₉₀ – minimum dose to 90% of high-risk clinical target volume, volume groups – patients sub-divided according to the volume of HR-CTV, PA – planning aim

Table 5. Occurrence of complications and local control at 3 months after brachytherapy

Complication	Whole study population							Tumor volume > 50cm ³						
	Group 1			Group 2			p-value	Group 1			Group 2			p-value
	n	N	%	n	N	%		n	N	%	n	N	%	
Intra-operative utero-vaginal complications	9	54	16.7	17	63	27.0	0.18	5	21	23.8	5	18	27.8	0.78
Any late complication	33	51	64.7	33	54	61.1	0.70	14	21	66.7	8	14	57.1	0.57
G3-4 late complications	7	51	13.7	7	54	13.0	0.91	3	21	14.3	3	14	21.4	0.66
GI complications	6	51	11.8	5	54	9.3	0.68	3	21	14.3	0	14	0.0	0.26
Complete response at 3 months	47	51	92.2	55	57	96.5	0.42	19	21	90.5	15	16	93.8	0.72

n – number of patients with mentioned features, N – number of patients with follow-up data available, GI complications – gastro-intestinal complications

Intra-operative utero-vaginal complications, mostly uterine perforations, occurred in 17% and 27% of cases in the groups 1 and 2, respectively ($p = 0.18$). Needle placement directly adjacent to OARs or suspected perforation of OARs occurred in 3.7% and 7.9% of cases, respectively ($p = 0.45$). However, none of these required specific treatment, and none of the cases presented with significant bleeding when the interstitial component was removed.

We analyzed available follow-up information to assess the impact of different treatment schedules on the clinical results for the whole study population, and separately for the group with largest tumors. No difference was detected in the local control at three months between the groups or in late complications (Table 5).

To analyze the costs, we randomly selected three patients from each group and considered as typical cases. The differences in costs were due to additional MRI and procedures with anesthesia in the group 2. The mean costs for two treatment weeks were €15,785 and €20,310, in the groups 1 and 2, respectively. Therefore, two fractions delivered with one applicator insertion resulted in approximately 22.3% of lower costs.

Discussion

This retrospective study investigated the effect of two different BT protocols, i.e., two BT fractions in one applicator insertion on consecutive days, repeated the following week, or a separate applicator insertion for each of the four fractions, with respect to the delivered radiation doses in 117 patients with locally advanced cervical cancer. According to the results, applicator insertions separately for each of the four BT fractions more frequently allowed the fulfillment of PAs of 85 Gy (hard constraint) and 90 Gy (soft constraint) to HR-CTV D₉₀, as compared with a schedule of four fractions with two applicator insertions.

In previous studies, it has been demonstrated that BT has an important role in the treatment of LACC, since BT improves local control and overall survival in comparison with external radio/chemotherapy alone [12-15]. Unified international instructions for contouring, dose optimization, and reporting as well as guidelines for dose planning aims for target volumes and OARs have been developed by the GEC-ESTRO GYN working group and EMBRACE study group [1,3,7,16]. However, there is still no globally recognized standardized fractionation scheme. A wide variety of regimens have been used by different institutions [8,9,17,18]. In Europe, due to the influence of EMBRACE study, a frequently used schedule involves four BT fractions of 7 Gy [19]. In the United States, the most common schedule for BT is four to five fractions of 5.5-6 Gy per fraction [20,21]. Low-income countries with lower resources and a significantly higher incidence of cervical cancer can face challenges with this expensive cancer treatment. This may result in protocols with fewer fractions and a larger dose per fraction [17,22,23]. In addition, due to COVID-19 and the need to save healthcare resources, an institution in Yale, USA, changed the schedule of BT to a single application: three fractions treated within one week with 8 Gy per fraction [24].

Evidence suggests that local control benefits from the delivered dose of 85 Gy to HR-CTV D₉₀, with the dose of 90 Gy further improving this result [25]. When evaluating treatment method in terms of dosimetric result, fulfilling PAs for a larger proportion of patients is a more informative parameter than the calculated mean dose of study population. In this study, the PAs were fulfilled significantly more often with four separate applicator insertions. The PA of 85 Gy was fulfilled in 83% and in 97% of cases, and the PA of 90 Gy in 67% and in 84% of cases with two and four insertions, respectively. According to the sub-group analysis, large tumors gained the most benefit from the four

insertions. In other words, this benefit from separate applications was emphasized in the most challenging cases.

Occasionally, it is very difficult to initially achieve a good position of the applicator and needles, because only MR image with the applicator *in situ* makes it easier to identify the best positions of interstitial needles to cover the target. Therefore, additional insertions of the applicator can help in achieving better doses.

However, in this study, the better delivered doses did not translate into better remission rates or decreased late toxicity. Comparably with previous studies, grade 3-4 late complications were observed in 13-14% and a complete response at 3 months in 92-97% of our study population. In the EMBRACE-1 study, grade 3-5 late complications were detected in 14.6% of patients, and 5-year local control was 92% [19]. Similarly, RetroEMBRACE study detected persistent disease after treatment in 13 out of 488 patients (complete response, 97%) [25].

Other institutions have previously reported a low-rate of severe intra-operative complications [26,27]. Nevertheless, four versus two invasive applicator insertion procedures potentially carries a higher risk of early complications. None of our patients experienced a severe intra-operative complication, despite the multiple applicator insertions.

Moreover, a negative side of additional applications is the higher price of a treatment. Therefore, by delivering two fractions with one insertion, it is possible to save costs relating to the procedure and anesthesia. There is evidence indicating that if the applicator is left in place overnight, it has an insignificant dosimetric effect on the delivered second dose [10]. Nonetheless, the position of the applicator and needles must not change between fractions, and this must be confirmed by imaging. Using CT imaging on the second day of treatment instead of MRI is more affordable. OARs (e.g., sigma) typically change position and need re-delineation. Previous studies have suggested that execution of a dose-optimized previous day plan of brachytherapy in subsequent fraction, resulted in an increase of D_{2cc} doses to OARs [28,29]. Therefore, the work of a medical physicist is required for image fusion, verifying the position of the applicator, and correcting the dose optimization. By contrast, being overnight with an applicator *in situ*, the patient also needs more care and analgesia, which reduces the savings mentioned above. Our analysis indicated that in typical cases, it is possible to save about 22% of the costs by keeping the applicator *in situ* overnight. However, if pain management is insufficient and the patient needs strong medication and more intensive monitoring, this reduces the savings.

The weakness of this study is that it was retrospective in nature, and data were collected over a long period of time (from 2009 to 2018). In addition, our institution's learning curve occurred at the beginning of the study period (this only refers to group 1 patients), and we also used more interstitial needles for group 2 patients, which is presumably an effect of longer experience. In the subgroup analysis, the groups were also small, which may have affected the results. Additionally, we could not analyze cost-effectiveness.

Conclusions

According to this study, four applications conferred the achievement of PA to HR-CTV, and larger tumors in particular gained the most benefit. However, no significant increase was observed in the risk of early complications resulting from a higher number of invasive procedures. Nevertheless, brachytherapy is a rather expensive treatment, so the advantages of multiple applications must be weighed against the costs.

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Disclosure

The authors report no conflict of interest.

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