Original paper

Comparative analysis of image-guided adaptive interstitial brachytherapy and intensity-modulated arc therapy versus conventional treatment techniques in cervical cancer using biological dose summation

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Abstract

Purpose: To compare image-guided adaptive interstitial brachytherapy (BT) and intensity-modulated arc therapy (IMAT) with conventional treatment techniques in cervical cancer using an alternative biological dose summation method.

Material and methods: Initially, 21 interstitial BT and IMAT plans of patients with cervical cancer were included and additional plans were created (inverse optimized interstitial, optimized intracavitary, non-optimized intracavitary BT plans, and conformal external beam radiotherapy [EBRT]). The most exposed volume of critical organs in BT were identified manually on EBRT CT images. Biological total doses (EQD2) were calculated and compared between each combination of BT and EBRT plans. This method was compared with uniform dose conception (UDC) in IMAT and conformal EBRT plans.

Results: The D_{90} of high-risk CTV and D_2 of bladder and sigmoid were different in BT techniques only: $p = 0.0149$, < 0.001, < 0.001, respectively. The most advantageous values were obtained in the interstitial treatment plans and inverse optimized interstitial plans did not differ dosimetrically from these, while optimized intracavitary plans resulted in worse dose-volume parameters, and the worst of all were intracavitary plans without optimization. The D_2 of rectum was significantly lower with IMAT than with conformal EBRT plans ($p = 0.037$) and showed the same trend in BT plans as the other parameters ($p < 0.001$). The UDC dose summation method overestimated D_2 of bladder, rectum, and sigmoid ($p < 0.001$ for all).

Conclusions: Although optimization improves the quality of conventional BT plans, interstitial plans produce significantly higher dose coverage of high-risk clinical target volume (HR-CTV) and lower doses to organs at risk (OARs). IMAT plans decrease the dose to the rectum. UDC overestimates OARs doses.

Purpose

The standard of care in the curative treatment of locally advanced cervical cancer (stages IB2-IVA) are external beam radiotherapy (EBRT) and intracavitary (ic.) or interstitial (is.) brachytherapy (BT) boost with concomitant chemotherapy. Both radiotherapy modalities have developed rapidly, with increasing sophisticated techniques appearing to escalate the dose to the tumor and spare organs at risk (OARs). These include intensity-modulated arc therapy (IMAT) [1] and image-guided adaptive interstitial brachytherapy (IGABT) [2,3]. In this situation, an accurate and reliable dose reporting is essential.

The use of BT boost has been linked with pelvic control and overall survival [4]. Adaptive, conformal BT approaches result in further improved clinical outcomes [5], with dose coverage of the target volume (D_{90}, the minimum dose delivered to 90% of the high-risk clinical target volume [HR-CTV]) correlating with local tumor control

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[2,6,7], and the minimal dose of the most exposed 2 cc of the OARs with normal tissue toxicity [8,9].

To report these dose-volume parameters properly, overall volumetric doses have to be integrated with EBRT and BT. As simple physical dose summation does not take into consideration the different biological effects, the equivalent dose given in 2 Gy fractions (EQD2) has to be calculated [10,11]. In the GEC-ESTRO recommendations, based on the EMBRACE study [12], the dose distribution of the EBRT is assumed to be completely uniform for the target volume and OARs (uniform dose conception – UDC) [13]. However, the EBRT dose is not always uniformly distributed. In the intensity-modulated radiotherapy (IMRT) technique, the most exposed 2 cc of the OARs is not a disjunct volume, since its voxels are dispersed in the organ, as we showed earlier [14]. In previous investigations, authors added BT and EBRT dose-volume histogram (DVH) of EQD2 doses [15] or made rigid image registration of BT and EBRT CT or MR images [16]. It was also shown before that the most exposed part of the OARs in the integrated plans evolves in the region where the maximum dose is in BT. However, this 2 cc is not in the same location as the most exposed part of EBRT [14]. Therefore, the simple DVH addition method sums the dose of two different 2 cc volumes. The rigid image registration technique does not take into account the deformation of the regions of interest and from this, doses of different tissues are summarized. Only deformable image registration (DIR) could be an appropriate method to integrate BT and EBRT doses for HR-CTV and OARs, but "currently no DIR program is capable of tracking the location and dose-exposure history of relevant biological structures within the target volumes and OARs" (ICRU report 89) [17]. The main problem is a foreign body (an applicator) in situ, which is not present on EBRT image data sets.

The aim of the present study is to present an alternative method for adding the biologically effective doses of EBRT and BT in the absence of adequate deformable registration algorithms and compare it to the recent UDC method. Using biological dose summation of the most exposed volumes of the critical organs, we compared IMAT and interstitial IGABT versus conventional treatment techniques in cervix cancer.

Material and methods

At our Institute, 21 interstitial IGABT and IMAT plans of patients with cervical cancer were included in this study. Selection criteria was stage IB2-IVA with poor response to EBRT. Patients were examined with pelvic magnetic resonance imaging (MRI) and staged with computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) at the beginning, and the therapeutic effect was assessed with an MRI at the end of EBRT. The EBRT was delivered with an energy of 10 MV using 2 full arcs. The prescribed dose was 1.8/50.4 Gy for the whole pelvis. Based on our local IGRT protocol, CBCT verification was made from 1st to 3rd fractions; the systematic error was calculated and corrected before the 4th fraction and weekly verification was completed for patient positioning. EBRT was complemented with BT boost, delivered with combined interstitial-intracavitary technique, starting 1 week after EBRT, given 1 or 2 fractions weekly. Because of a given EBRT boost or due to a weak condition, thirteen patients were treated with 4 BT fractions of 7 Gy, five with 3, two with 2, and one with 1 fraction. Initial and post- EBRT MRI were used to determine the number and position of needles in the ring or Fletcher type interstitial applicator [18,19,20]. The implantation was transrectal US-guided. The delineation of HR-CTV of bladder, rectum, sigmoid, and bowel was performed on post-implant CT, using information of post-EBRT MRI. During treatment planning, manual optimization (MO) was used to achieve an optimal dose distribution. In clinical routine, the EUD method was used to determine the dose constraints for HR-CTV and OARs in remaining BT fractions. The total doses were also calculated with this method [21,22].

Besides manual optimized interstitial (MO_{IS}) and IMAT treatment plans, additional BT and EBRT plans were created:

- In inverse optimized interstitial BT plans (IO_{IS}), only the HIPO (hybrid inverse planning optimization) dose-volume-based algorithm was used. The weight of different DVH constraints (cost functions) was tuned to achieve optimal dose distribution;
- Manual optimized intracavitary BT plans (MO_{IC}) were 3D optimized (based on CT), but without using the needles. Dose was prescribed to points A and manual optimization was used;
- Non-optimized intracavitary BT plans (NO_{IC}) dosimetry was based on points A without optimization;
- Conformal EBRT plans (CONF) used the conventional 4 field box technique, with 18 MV photon beams.

Since the most exposed part of the OARs is in the region where the maximum dose is in BT, the most exposed 2 cc of bladder, rectum, and sigmoid were determined in BT CTs (Oncentra Brachy v. 4.5.3, Elekta Brachytherapy, Veendendaal, The Netherlands). Subsequently, these most exposed 2 cc from BT were manually identified on EBRT CT images for every patient (Eclipse v. 13.7, Varian Medical Systems, Palo Alto, USA) (Figure 1). We investigated BT and EBRT CT image sets on the same monitor in axial, sagittal, and coronal views, and delineated 2 cc volume on EBRT CT in the same anatomical place where the isodose surface of the dose of the most exposed 2 cc was found in the BT CT. To reduce subjectivity, one BT expert physicist along with one radiation oncologist (experienced in gynecologic BT) performed this critical part of the investigation.

The total EQD2 doses of these volumes were calculated in each combination of BT and EBRT plans using the linear-quadratic radiobiological model. The α/β of HR-CTV was assumed 10 Gy, while for OARs, 3 Gy was used. The following dose-volume parameters were used for quantitative evaluation of plans:

- D_{90}: the minimum dose delivered to 90% of HR-CTV (Gy);
- $D_2(x)$: the minimal dose of the most exposed 2 cc of the critical organ x (Gy),
  where x is the bladder (b), rectum (r), or sigmoid (s).
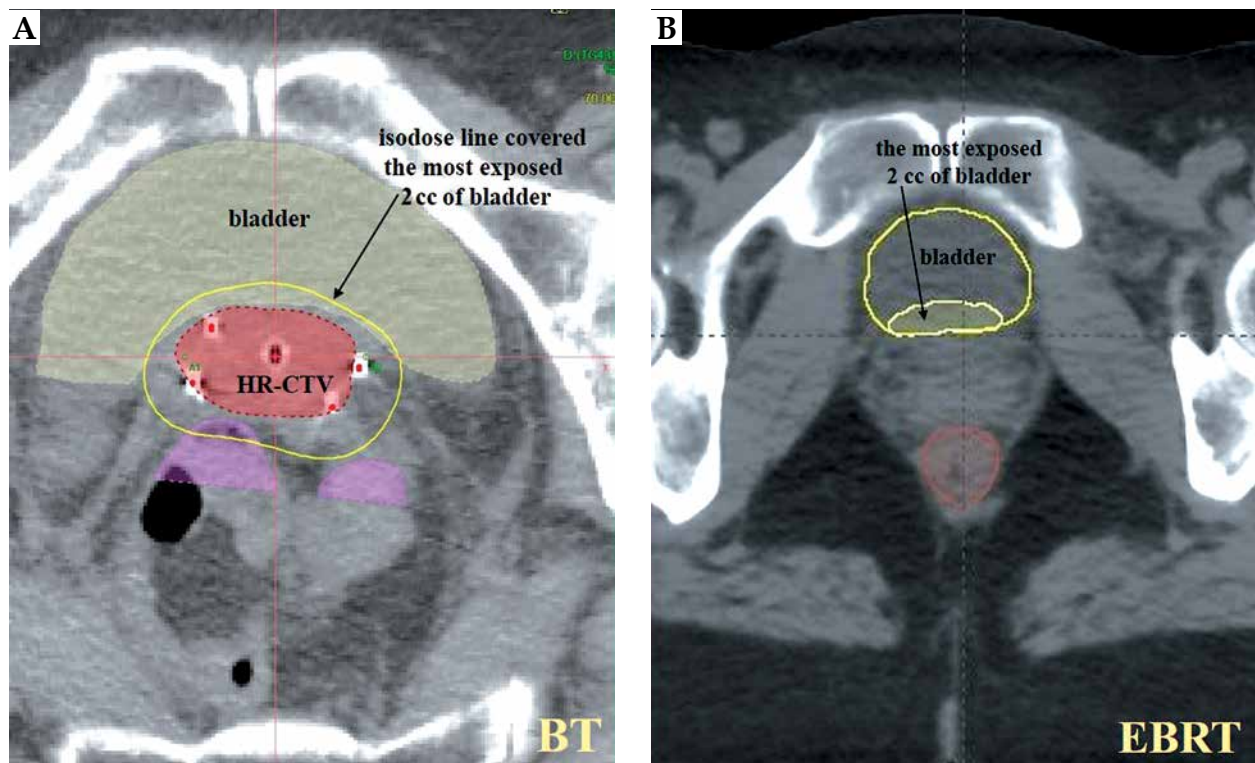
Fig. 1. The most exposed 2 cc of bladder in BT (**A**) contoured in EBRT CT (**B**) in an axial slice

Two-way ANOVA and Fisher-LSD (least significant difference) post-hoc tests were used (Statistica 12.5, StatSoft, Tulsa, OK, USA) to compare biological total dose of different treatment combinations:

- IMAT EBRT + MO_{IS} BT,
  - + IO_{IS} BT,
  - + MO_{IC} BT,
  - + NO_{IC} BT;
- CONF EBRT + MO_{IS} BT,
  - + IO_{IS} BT,
  - + MO_{IC} BT,
  - + NO_{IC} BT.

This dose summation method was compared with UDC in combined MO_{IS} BT plans and IMAT, or conformal EBRT plans using Wilcoxon-matched pairs test.

Results

The mean volume of the HR-CTV after EBRT (residual tumor volume) was 46.1 cc (range, 24.1-100.2 cc). Comparing different combinations of BT and EBRT plans, we found that D_{90} of high-risk CTV and D_2 of bladder and sigmoid were different in BT techniques only: $p = 0.0149$, < 0.001, < 0.001, respectively. The most advantageous values were obtained in the MO_{IS} plans. IO_{IS} plans did not differ dosimetrically from these plans, while MO_{IC} plans resulted in worse dose-volume parameters, and the worst of all were NO_{IC} plans (Table 1). The D_2 of rectum was significantly lower with IMAT than with CONF EBRT plans ($p = 0.037$) and showed the same trend in BT plans as the other parameters ($p < 0.001$). D_2(r) were 40.0 Gy, 38.4 Gy, 44.9 Gy, and 72.1 Gy for IMAT and MO_{IS}, IO_{IS}, MO_{IC}, and NO_{IC} combinations, respectively, and 49.0 Gy,
47.3 Gy, 53.8 Gy, and 81.1 Gy for CONF EBRT and MO_{IS}, IO_{IS}, MO_{IC}, and NO_{IC} plans (Figure 2).

The post-hoc test showed significant differences in all variables between is. (MO_{IS} and IO_{IS}) and ic. (MO_{IC} and NO_{IC}) BT plans, while D_2(b) and D_2(r) differed between MO_{IC} and NO_{IC} plans.

It was found that the HR-CTV was exposed at least with the recommended EQD2 total dose (85 Gy) in 86% of the patients with the IMAT + MO_{IS} IGABT technique. With the IO_{IS}, MO_{IC}, and NO_{IC} plans, this was only 79%, 64%, and 71%, respectively. The same proportions were derived with CONF EBRT. In 86% of the patients, the D_2 rectal dose was below recommended tolerance dose in MO_{IS} BT and IMAT or CONF EBRT plans, while for IO_{IS} BT plans, it was 86% and 79%, for MO_{IC} plans 79% and 71%, and NO_{IC} BT plans only 43% and 36%, respectively (Table 1).

Comparing our dose summation method to UDC in IMAT and CONF EBRT plans, we found that the UDC overestimates D_2 of bladder by 12% and 8.5%, rectum by 55% and 26.5% (Figure 3) and sigmoid by 17.2% and 12%, respectively. Detailed EQD2 and *p* values are presented in Table 2.

Discussion

Brachytherapy boost has a fundamental role in the radiotherapy of locally advanced cervical cancer [23]. Presently, there are no better alternatives [1,24]; however, several high-tech EBRT techniques are possible competitors such as conformal [25], image-guided [1] and intensity-modulated EBRT [26,27], arc therapy [28], helical tomotherapy [29], and stereotactic radiotherapy with linear accelerators [30,31,32] or with CyberKnife [33].

Table 1. Mean EQD2 total doses of different combinations of BT and EBRT plans

| EQD2		MO_{IS}	IO_{IS}	MO_{IC}	NO_{IC}	p^* (TT)	p^* (BT)
D_{90} (HR-CTV) (Gy)	IMAT	84.6 (86%)	84.3 (79%)	82.2 (64%)	88.7 (71%)	0.9899	0.0149
	CONF	84.6 (86%)	84.3 (79%)	82.2 (64%)	88.7 (71%)		
$D_2(b)$ (Gy)	IMAT	62.9 (93%)	62.5 (93%)	71.5 (79%)	88.4 (36%)	0.434	< 0.001
	CONF	64.9 (93%)	64.6 (100%)	73.6 (71%)	90.5 (36%)		
$D_2(r)$ (Gy)	IMAT	40.0 (86%)	38.4 (86%)	44.9 (79%)	72.1 (43%)	0.037	< 0.001
	CONF	49.0 (86%)	47.3 (79%)	53.8 (71%)	81.1 (36%)		
$D_2(s)$ (Gy)	IMAT	55.3 (100%)	54.4 (100%)	60.5 (82%)	71.2 (64%)	0.2794	< 0.001
	CONF	57.9 (100%)	56.9 (100%)	63.5 (64%)	73.8 (55%)		

MO_{IS} – manual optimized interstitial, IO_{IS} – inverse optimized interstitial, MO_{IC} – manual optimized intracavitary, NO_{IC} – non-optimized intracavitary BT plans, IMAT – intensity-modulated arc therapy, CONF – conformal EBRT plans, D_{90} – the minimum dose delivered to 90% of HR-CTV, $D_2(b)$, $D_2(r)$, $D_2(s)$ – the minimal dose of the most exposed 2 cc of bladder, rectum, and sigmoid
*In brackets: percentage of plans, which fulfilled the criteria of GEC-ESTRO Recommendation. *2-way ANOVA and Fisher-LSD post-hoc test*
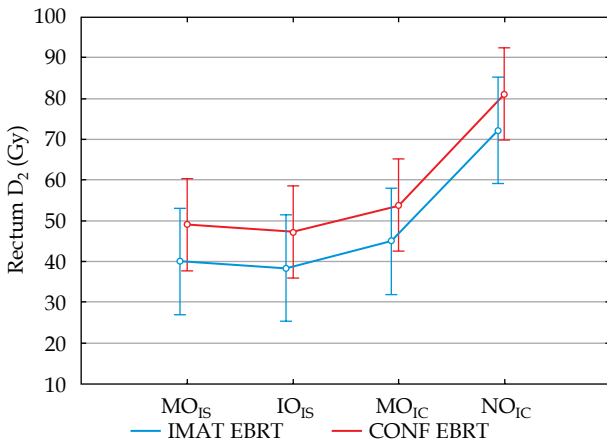
Fig. 2. Total EQD2 of the most exposed 2 cc of rectum in combinations of intensity-modulated arc therapy (IMAT) or conformal (CONF) EBRT and manual optimized interstitial (MO_{IS}), inverse optimized interstitial (IO_{IS}), manual optimized intracavitary (MO_{IC}), and non-optimized intracavitary (NO_{IC}) BT plans
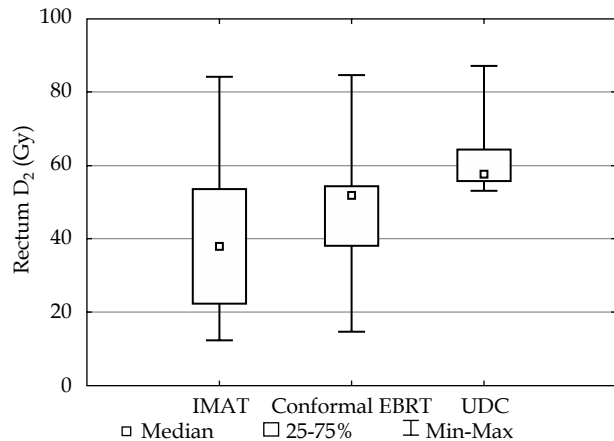
Fig. 3. Total EQD2 of the most exposed 2 cc of rectum in interstitial brachytherapy and intensity-modulated arc therapy (IMAT) or conformal (CONF) EBRT using our dose summation method and using uniform dose conception (UDC)

Table 2. The EQD2 total doses of interstitial BT plus intensity-modulated arc therapy (IMAT) or conformal (CONF) EBRT plans and the same parameters calculated by the UDC method

	D_{90} (HR-CTV) (Gy)	$D_2(b)$ (Gy)	$D_2(r)$ (Gy)	$D_2(s)$ (Gy)
IMAT	84.6	62.9	40.0	55.3
p^*	0.6547	< 0.001	0.0012	0.0033
CONF	84.6	64.9	49.0	57.9
p^*	0.6547	< 0.001	< 0.001	0.0081
UDC	84.5	70.4	62.0	64.8

*D_{90} – the minimum dose delivered to 90% of HR-CTV, $D_2(b)$, $D_2(r)$, $D_2(s)$ – the minimal dose of the most exposed 2 cc of bladder, rectum, and sigmoid. *Wilcoxon-matched pairs test*

Although MRI-based BT has been considered the 'gold standard' by international recommendations [13], in the lack of its broad availability, CT-based contouring and planning can also lead to similar dosimetrical and clinical results with the use of post-EBRT MRI [34,35,36].

The latter case has an advantage over MRI-based BT: image registration is easier between post-implant CT and EBRT CT than between post-implant MRI and EBRT CT. At this moment, DIR is not yet available even between similar imaging modalities. The fundamental reasons are

the foreign body (plastic or metal applicator) *in situ* and the deformation of organs due to application. Other authors added BT and EBRT DVHs directly [15] or used rigid image registration [16] instead of DIR. We mimicked DIR 'in mind' by defining the most exposed 2 cc of critical organs in BT CT, and then delineating this volume on EBRT CT. In this way, the addition of biological doses of the same volumes (2 cc) became possible without software image registration. Obviously, this manual delineation has also limitations such as inter-observer variability. It is a time-consuming method, and identification of these 2 cc volumes is not trivial with different bladder and rectal filling.

Gelover *et al*. [15] did not find statistically significant differences between EQD2 doses of OARs in conformal and IMRT EBRT techniques by adding EBRT and BT DVHs; however, they did not add the dose of the same volumes of OARs. In our analysis, D_2 (EQD2) of the rectum was significantly lower by 9 Gy (on average) in IMAT than in CONF EBRT plans. This may be due to the fact that the most exposed volumes of OARs are not identical in the IMAT and CONF plans, since the dose of critical organs can be decreased with the IMAT technique, as is shown in Figure 4.

The effect of BT technique on dose-volume parameters was also investigated in our study. Of note, all examined dosimetric parameters were statistically significant. The most valuable plans were obtained using MO_{IS} and IO_{IS}, while MO_{IC} resulted in worse dose-volume parameters, and the worst of all were NO_{IC} plans. Conventional A-point-based (NO_{IC}) plans often resulted in an overdosage of the HR-CTV (D_{90} 88.7 vs. 82.2 Gy) compared to MO_{IC} plans, but with higher doses to OARs. Paul *et al*. demonstrated that the dosimetric advantages of volume-based intracavitary planning produced more conformal plans than point-A-based plans. Volume-based plans resulted in a 6-12% reduction in the total dose to 2 cc of the OARs as well as an 8-37% reduction per BT fraction compared to point-A-based plans [37]. Previous studies have pointed out the strong correlation between local tumor control and D_{90} of HR-CTV, with the best results above 85 Gy EQD2 [24]. In our case, 86% of the patients received at least this dose during the treatment (IMAT + MO_{IS} BT). Patients who received EBRT boost and fewer fractions of BT are the 'underdosed' cases, with a D_{90} of 79.2 Gy. However, for standard fractionation, D_{90} is 90.1 Gy (*p* = 0.0006). As the HR-CT is an integral part of the target volume in EBRT plans and the same constraint was used for IMAT and for CONF EBRT (95% of prescribed dose has to cover 95% of the planning target volume homogeneously), no differences in the coverage of the HR-CTV were noted. The D_2 OARs doses are the predictors of side effects. In 86% of cases, rectal D_2 remained below recommended tolerance level during the treatment, though this proportion would have been only 43% using NO_{IC} BT, and 36% with NO_{IC} BT and CONF EBRT. Moreover, the effect of the BT technique used is also larger than the EBRT technique. Van de Kamer *et al*. [16] showed that without EBRT boost, DVH parameter adding is a good approximation method, but underestimates D_{90} by 2.8%. They
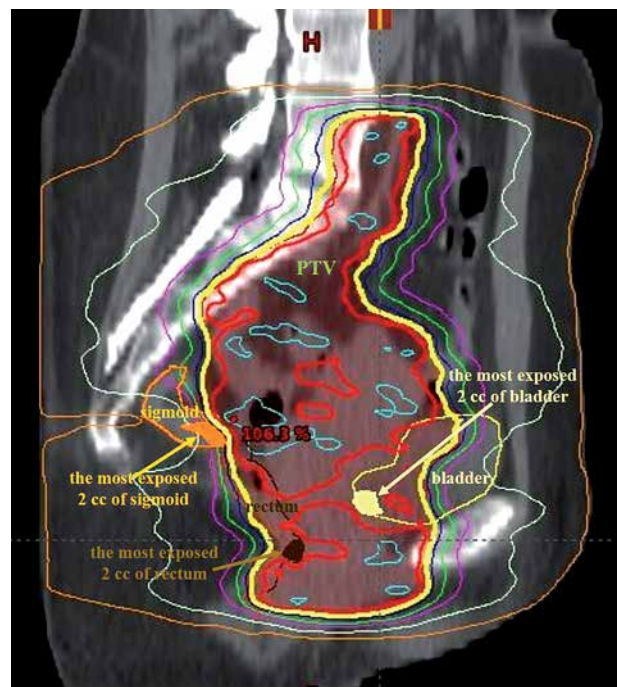
Fig. 4. The most exposed 2 cc of bladder (yellow), rectum (brown), and sigmoid (orange) from BT in a sagittal CT slice in an intensity-modulated arc therapy plan. Red line: 100%; yellow: 95% isodose line

used rigid image registration, and only 5 patients were investigated in this study. Our dose summation method showed that UDC overestimates D_2 of bladder, rectum, and sigmoid in both EBRT techniques. The maximal deviation was 22 Gy (D_2(r)). There was no difference between plans with or without EBRT boost, but there were only 8 cases of the former.

Overall treatment time (OTT) is another influential factor of tumor control; 85 Gy should be delivered to HR-CTV within 50 days [23]. At our Institute, it takes 61 days (on average), and we are planning to introduce OTT factor into our dose summation technique.

This study is the starting point of the development of an algorithm for the summation of EBRT and BT biologically effective doses, which uses an artificial intelligence-based DIR algorithm to match the critical anatomical structures in the two radiotherapy modalities. Further investigations are needed to review whether our method better predicts toxicity than the recent UDC method.

Conclusions

A comparison between interstitial IGABT and IMAT versus conventional treatment techniques in the treatment of cervical cancer using our biological dose summation method shows that interstitial optimized BT plans resulted in a significantly higher dose coverage to the HR-CTV and lower doses to the OARs, while IMAT decreases the rectal dose. UDC overestimates the OARs doses compared to a manual definition of D_2 in the EBRT plans.

Disclosure

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