Image guided radiation therapy boost in combination with high-dose-rate intracavitary brachytherapy for the treatment of cervical cancer

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Abstract

**Purpose:** The purpose of this study was to demonstrate the dosimetric and clinical feasibility of image guided radiation therapy (IGRT) combined with high-dose-rate (HDR) intracavitary brachytherapy (ICBT) to improve dose distribution in cervical cancer treatment.

**Material and methods:** For 42 cervical cancer patients, magnetic resonance imaging (MRI) scans were acquired after completion of whole pelvic irradiation 45-46 Gy and 5 fractions of B + I (ICBT + IGRT) treatment were subsequently received. The high risk clinical target volume (HRCTV), intermediate risk clinical target volume (IRCTV), bladder, rectum, and sigmoid were contoured on the computed tomography (CT) scans. The total planning aim doses for HRCTV was D90% > 85 Gy, whilst constraints for rectum and sigmoid were D2cc < 75 Gy and D2cc < 90 Gy for bladder in terms of an equivalent dose in 2 Gy (EQD2) for external beam radiotherapy (EBRT) and brachytherapy boost. The IGRT plan was optimized on top of the ICBT dose distribution. A dosimetric comparison was made between B + I and optimized ICBT (O-ICBT) only.

**Results:** The mean D90% of HRCTV was comparable for B + I and O-ICBT (p = 0.82). For B + I plan, HRCTV D100%, IRCTV D100%, and ICBT D90% were significantly increased by a mean of 10.52 Gy, 5.61 Gy, and 2.70 Gy, respectively (p < 0.01). The D2cc for bladder, rectum, and sigmoid were lower by a mean of 21.36, 6.78, and 10.65 Gy, respectively (p < 0.01). The mean rectum V60 Gy value over 42 patients was almost the same for both techniques but for bladder and sigmoid B + I had higher V60 Gy mean values as compared with the O-ICBT.

**Conclusions:** B + I can improve dose distribution in cervical cancer treatment; it could be useful for tumors extended beyond the reach of intracavitary/interstitial brachytherapy (IC/ISBT) or for centers that are inexperienced or ill-equipped with IC/ISBT techniques. Additional confirmatory prospective studies with larger numbers of patients and longer follow-up are required to validate the durability.

**Key words:** cervical cancer, HDR brachytherapy, IGRT.
in patients with bulky or an obliterated endocervical canal, vaginal spread disease; it can be combined with ICBT by placing needles in the parametrial region or in large tumor. Intracavitary/interstitial brachytherapy (IC/ISBT) can achieve good target coverage and is currently recommended as a standard [13,14,15,16].

In the present study, we provided an alternative technique to boost the parametrial region or large unfavorable tumor. We integrated ICBT with a simultaneous image guided radiation therapy (IGRT) boost to improve target dose coverage and spare of the OARs. We abbreviated this technique to B + I (ICBT + IGRT). The dosimetric and clinical feasibility of this technique was demonstrated. A dosimetric comparison was made between B + I and optimized ICBT (O-ICBT) only. B + I technique could be useful for tumors extended beyond the reach of IC/ISBT or for centers that are inexperienced or ill-equipped with IC/ISBT techniques.

Material and methods
Forty-two patients with large or topographically unfavorable tumors were included in this study. The patients were 39-63 years of age at the time of treatment (median 49). All tumors were squamous cell carcinomas, consisted of FIGO (International Federation of Gynecology and Obstetrics) stage IIB-IVA (18 IIB, 7 IIIA, 11 IIIB, 6 IVA).

Magnetic resonance imaging (MRI) scans were acquired after whole pelvic EBRT 45-46 Gy, and subsequently 5 fractions of B + I radiation boost were performed based on the MRI and gynecologic examination. At time of brachytherapy, the median volumes of high risk clinical target volume (HRCTV) and intermediate risk clinical target volume (IRCTV) for the 42 cases were 62.88 ± 21.94 cm³ and 145.15 ± 36.36 cm³, respectively.

For each fraction, a bladder catheter was used to control bladder filling and a Fletcher applicator (Elekta AB, Stockholm, Sweden) was inserted. The applicator was subsequently fixed to a board, which can slide between the mobile bed, the treatment couch, and the computed tomography (CT) couch. A vacuum bag and a thermostatic mask were used to fix the patient position and then a CT scan was obtained. There was no image fusion between CT and previous MRI scans because of organ deformations. The targets (HRCTV and IRCTV) were identified from CT and delineated by the radiation oncologist on the CT scans. The OARs (bladder, rectum, and sigmoid) were contoured according to the framework of the international study on MR-guided brachytherapy in locally advanced cervical cancer (EMBRACE) (see http://www.embracestudy.dk). No margins were added to targets and OARs, since the setup uncertainties and internal motions were minimal.

The total EBRT and brachytherapy boost doses were evaluated in terms of equivalent dose in 2 Gy fractions (EQD2), using $\alpha/\beta = 3$ Gy for OARs and $\alpha/\beta = 10$ Gy for targets. We define $D_x$ (or $D_x(%)$) as the dose expressed in Gray (Gy) received by $x$ volume in cc (or $x$% of the total volume), and $V_y$ Gy the volume expressed in percentage that receive $y$ Gy. The treatment planning aim was to obtain $D_{90\%} > 85$ Gy for HRCTV and $D_{90\%} > 75$ Gy for IRCTV from EBRT and $B + I$ boost. Dose volume constraints for OARs were $D_{2cc} < 90$ Gy for the bladder and $D_{2cc} < 75$ Gy for rectum and sigmoid. It was assumed that the $D_{2cc}$ of all three OARs were exposed to the full EBRT dose of 45 Gy. We can calculate physical dose objectives and constraints per fraction by the equation [17]:

$$\text{EQD}_2 = n \left(1 + \frac{d}{\alpha/\beta}\right) / \left(1 + \frac{2}{\alpha/\beta}\right)$$

where $n$ is the number of fraction, $d$ is the dose per fraction, and $\alpha/\beta$ is the $\alpha/\beta$-ratio of the organ concerned. The calculated physical dose objectives were 6 Gy per fraction for HRCTV and 5 Gy per fraction for IRCTV, while the calculated $D_{2cc}$ OARs constraints were 5.4 Gy per fraction for bladder and 4.2 Gy per fraction for rectum and sigmoid. In clinical practice, bladder $D_{2cc}$ was optimized less than 5 Gy, since we wanted bladder $D_{2cc}$ lower than IRCTV dose objective.

The ICBT treatment plan was performed with the Oncentra® Brachy V4.3 treatment planning system (Elekta AB, Stockholm, Sweden) and the applicator reconstruction was done according to the GEC-ESTRO (Groupe Européen de Curiethérapie - European Society for Radiotherapy and Oncology) guidelines [18]. For $B + I$ plan, the prescription of the ICBT plan was 5 Gy per fraction and 3D graphical optimization was performed with the aim of optimizing the dose coverage of the target, while not reaching the dose constraint for OARs (5 Gy for bladder and 4 Gy for rectum and sigmoid) in order to allow an additional dose contribution from the IGRT boost. For O-ICBT plan, inverse planning simulated annealing (IPSA) optimization was used to optimize dose distribution. The planning aim was to obtain at least 85 Gy for $D_{90\%}$ in HRCTV.

For $B + I$ plan, the target dose coverage was always limited by the dose constraint of the OARs. If a sufficient dose to the target could not be achieved, a seven or nine field IMRT plan was produced with the Oncentra® External Beam V4.3 treatment planning system (Elekta AB, Stockholm, Sweden). The IMRT plan was optimized on top of the ICBT plan using an inverse dose optimization tool, which allows the use of dose volume histograms (DVHs) constraints on the total dose of ICBT and IMRT. The fields entrances were different in order to avoid a highway of dose through the patient and no upper dose constraint to targets was used when optimizing the boost plan.

The $B + I$ and O-ICBT plan were evaluated three dimensionally to determine the targets dose coverage and the sparing of OARs. $D_{90\%}, D_{95\%}$, and $D_{95\%}$ were used for targets comparison, while $D_{2cc}$ and V60 Gy were considered for OARs. V60 Gy represented the volume irradiated to more than 60 Gy (EQD2) by the accumulated dose from EBRT and brachytherapy boost. The boost plans physical isodose level was 2.65 Gy per fraction, since 45 Gy plus $5 \times 2.65$ Gy corresponds to 60 Gy in EQD2 dose. Dose volume histogram cutoff points above described for targets and OARs were compared between the $B + I$ and O-ICBT to show the dosimetric characteristics of $B + I$ technique.

High-dose-rate (HDR) brachytherapy treatment plan was performed after the $B + I$ dose planning and execu-
tion time varied from a few minutes to tens of minutes according to the source activity. When HDR brachytherapy treatment finished, the patient was transferred to an accelerator (Synergy®, Elekta AB, Stockholm, Sweden) with the applicator still in situ. The IGRT boost was guided by the applicator position on cone beam computed tomography (CBCT). Because the ICBT dose distribution was defined by the position of the applicator, this procedure ensured that the IGRT dose gradients were aligned with the ICBT dose gradients. The applicator was not removed until the IGRT boost finished to minimize any tissue movement and deformation. This procedure was repeated twice a week as scheduled for the conventional brachytherapy treatments performed in our institution.

Results

It was technically feasible to combine ICBT and IGRT dose distributions. An example is shown in Figure 1. The dose contribution from both the ICBT and IGRT is displayed. The ICBT plan was modified to keep the dose to OARs at physical dose constraint while keeping the target covered by the prescription dose as optimal as possible. Image guided radiation therapy boost plan gave dose to the part of the target, which was not covered by the ICBT plan. B + I plan presented substantially better target coverage while keeping the OARs at reasonably low doses. Table 1 shows mean and standard deviation (SD) in total EQD2 dose delivered by B + I and O-ICBT. For targets, HRCTV mean D90% was comparable for B + I and O-ICBT (p = 0.897); for B + I plan, the HRCTV D100%, IRCTV D100%, and D90% were significantly increased by a mean of 10.52 Gy, 5.61 Gy, and 2.70 Gy respectively, if compared with O-ICBT (p < 0.01), whereas the O-ICBT delivered higher D50% doses for targets with statistically significant difference. For OARs, bladder, rectum, and sigmoid doses were lower by a mean of 21.36, 6.78 and 10.65 Gy, respectively, for B + I as compared with O-ICBT. With O-ICBT plan, 6, 11, and 11 patients violated D2cc constraints for the bladder, rectum, and sigmoid, respectively (maximum value 93.35 Gy for bladder, 81.60 Gy for rectum, and 79.64 Gy for sigmoid). V60 Gy

Fig. 1. A sample dose distribution from intracavitary brachytherapy (ICBT) (A), image guided radiation therapy (IGRT) (B), and B + I (ICBT + IGRT) (C) plan for one fraction
IGRT boost in combination with HDR intracavitary brachytherapy

for rectum was almost the same but it was substantially higher for bladder and sigmoid in the B + I plan as compared with the O-ICBT plan. Figure 2 shows typical DVHs for HRCTV, IRCTV, bladder, rectum, and sigmoid for B + I and O-ICBT techniques.

Discussion

Brachytherapy takes advantage of the inverse square law in that high doses of radiation are given to the target and low doses are applied to the healthy tissues. Current use of the tandem ovoid or tandem ring applicator may not adequately cover the clinical target volume for cervical cancer, especially in the parametrial region or in the significant residual tumor site. In this study, we demonstrated that it was technically possible to combine IGRT and HDR ICBT in the treatment of cervical cancer. By adding dose from IGRT to the ICBT dose distribution, B + I improved the dose to the target significantly without compromising the constraints for OARs.

Bladder, rectum, and sigmoid are the most sensitive structures to damage during cervical cancer treatment. Georg et al. studied dose effect relationship for late side effects of the rectum and bladder in cervical cancer brachytherapy. They demonstrated that the increase of $D_{2cc}$ in OARs may be translated clinically to an increased probability of late side effects, especially if the $D_{2cc}$ value was close to the specific OARs constraint [19]. In this study, LQ model (EQD2) was used to calculate the targets planning aim dose and OARs dose constraints for B + I. It was theoretically possible to cover target volume while respecting the OARs dose constraints. For cervical cancer patients in our institution, 4 fractions of a boost dose of 5-6 Gy/fraction for HRCTV was recommended. This study highlighted that we can keep OARs doses at reasonably low level, treating patients for 5 fractions with a 6 Gy/fraction dose boost. The mean $D_{2cc}$ for bladder, rectum, and sigmoid was 74.43 Gy, 70.12 Gy, and 70.62 Gy, respectively. Cervical cancer patients with residual malignant cells detected at final stage of brachytherapy may benefit from this technique.

In this study, the HRCTV $D_{100\%}$, IRCTV $D_{00\%}$, and $D_{90\%}$ were significantly improved using B + I as compared with O-ICBT. The HRCTV $D_{90\%}$ is about 25% higher than $D_{90\%}$, which means that the tumor receives an inhomogeneous dose similar to that delivered with ICBT (35%), see Table 1. For locally advanced cervical cancer, the advanced

| Table 1. EQD2 dose comparison between B + I (ICBT + IGRT) and optimized ICBT (O-ICBT) for targets and OARs for 42 patients. The mean and SD values are listed for each parameter. P-value corresponds to pair-wise comparison |
|-------------------------------------------------|-----------|-----------------|--------|
| B + I                                           | O-ICBT    | p-value         |
| HRCTV $D_{100\%}$ 71.01 Gy (1.57)               | 60.49 Gy (2.19) | < 0.01          |
| HRCTV $D_{90\%}$ 84.97 Gy (1.65)                 | 84.90 Gy (0.63) | 0.82            |
| HRCTV $D_{50\%}$ 106.29 Gy (5.69)               | 114.63 Gy (7.84) | < 0.01          |
| IRCTV $D_{100\%}$ 61.99 Gy (1.18)               | 56.38 Gy (1.38) | < 0.01          |
| IRCTV $D_{90\%}$ 76.52 Gy (0.58)                 | 73.82 Gy (3.04) | < 0.01          |
| IRCTV $D_{95\%}$ 90.69 Gy (2.81)                | 99.81 Gy (4.57) | < 0.01          |
| Bladder $D_{2cc}$ 74.73 Gy (2.07)                | 86.09 Gy (3.27) | < 0.01          |
| Rectum $D_{2cc}$ 70.12 Gy (2.00)                 | 72.90 Gy (4.03) | < 0.01          |
| Sigmoid $D_{2cc}$ 70.62 Gy (3.19)                | 73.27 Gy (3.58) | < 0.01          |
| Bladder V60 Gy 52.84 cc (8.68)                   | 44.19 cc (6.75) | < 0.01          |
| Rectum V60 Gy 19.80 cc (4.76)                    | 18.63 cc (3.48) | 0.07            |
| Sigmoid V60 Gy 30.74 cc (8.86)                   | 19.25 cc (5.39) | < 0.01          |

HRCTV – high risk clinical target volume, IRCTV – intermediate risk clinical target volume, $D_{100\%}$, $D_{90\%}$, $D_{50\%}$ – the minimum dose received by 100, 90, and 50% of the prostate volume, $D_{2cc}$ – minimum dose to the most exposed 2 cm$^3$, V60 Gy represents the volume irradiated to more than 60 Gy (EQD2) by the accumulated dose from EBRT and brachytherapy boost

![Fig. 2. Comparison of a typical dose volume histograms (DVHs) for B + I (ICBT + IGRT) (solid line) and optimized ICBT (O-ICBT) (dashed line) techniques](image-url)
age of ICBT in the boost is maintained in B + I. For what is concerning OARs, the D_{2cc} standard deviation for bladder, rectum, and sigmoid in B + I was 2.07 Gy, 2.00 Gy, and 3.19 Gy, respectively. We can therefore conclude that the dose to OARs could be controlled within safe limits independently from the tumor location and size.

Parametrial involvement carries poor prognosis; bilateral external beam radiotherapy fields with midline block and IC/ISBT are commonly used to boost parametrical extension [11,20]. Mohamed et al. [21] compared doses delivered by ICBT plus EBRT parametrial boost (PB) with dose delivered by IC/ISBT. With the EBRT PB scenario, patients received lower mean values of HRCTV (PB) with dose delivered by IC/ISBT. With the EBRT PB doses delivered by ICBT plus EBRT parametrial boost parametrial extension [11,20]. Mohamed block and IC/ISBT are commonly used to boost parametrical external beam radiotherapy fields with midline independently from the tumor location and size.

The dose to OARs could be controlled within safe limits for gynecological applications are encouraging, more detailed studies on practical aspects of precision dose delivery need to be performed. Firstly, the cervix is not a fixed pelvic organ, rather one that is subject to movement during treatment [28,29]. It was assumed that the target moves together with the applicator and the applicator was fixed to a board so that applicator guided IGRT would minimize setup uncertainties. Secondly, bladder filling has a large impact on the surrounding organs [30,31]. In the B + I technique, a bladder catheter was used to control bladder filling, so that the bladder volume was the same during HDR ICBT and IGRT delivery. Thirdly, the IGRT boost plan was delivered immediately after the ICBT with the applicator still in situ, which enabled a precise intersection of IGRT and ICBT dose distributions. Cone beam computed tomography can minimize the uncertainty of patient position; rectum and sigmoid movement was assessed visually on CBCT in as much detail as CBCT image quality allowed.

Conclusions

It was technically feasible to combine ICBT and IGRT by optimizing the IGRT boost on top of the ICBT dose distribution. The B + I technique not only provides excellent target coverage but also maintains low doses (D_{2cc}) to the OARs. It was dosimetrically and logistically feasible to use B + I to boost parametrical region or large unfavorable tumor. B + I technique offers an alternative solution to boost very unfavorable topography and extensive disease where the needles may be too challenging to be inserted for full dose coverage. Additional confirmatory prospective studies with larger numbers of patients and longer follow-up are required to validate the durability of these results.

Disclosure

Authors report no conflict of interest.

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