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MRI guided brachytherapy

Intra-fraction uncertainties of MRI guided brachytherapy in patients with cervical cancer

Christel N. Nomden [a,*], Astrid A.C. de Leeuw [a], Judith M. Roesink [a], Robbert J.H.A. Tersteeg [a], Henrike Westerveld [b], Ina M. Jürgenliemk-Schulz [a]

[a] University Medical Centre Utrecht, Department of Radiation Oncology; and [b] Academic Medical Centre, Department of Radiotherapy, Amsterdam, The Netherlands

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ABSTRACT

Dosimetric intra-fraction uncertainties in MRI-guided brachytherapy were analysed for HR-CTV and OARs. While dose differences were generally small, individual outliers occurred. In contrast to HDR, patients treated with PDR show increased mean rectal dose over time. Re-imaging prior to dose delivery helps to detect unfavorable anatomical changes, and allows for intervention.

Repetitive MR-imaging during brachytherapy (BT) of cervical cancer patients provides insight into movement and deformation of adjacent organs. Several groups have recently published the impact of changing anatomy on the delivered dose [1–4]. In these studies, MR-imaging was performed both after applicator insertion for treatment planning, and prior to dose delivery. In the present study, additional MR-images were acquired prior to and directly after high dose rate (HDR) BT dose delivery. This was achievable due to a 1.5 Tesla scanner integrated in the BT theatre. We investigated the dosimetric intra-fraction uncertainties by re-calculating the dose parameters for target and OARs volumes before and after HDR irradiation. Furthermore, we compared these HDR data with data of pulsed dose rate (PDR) treated patients of an earlier cohort study.

Materials and methods

Fifteen consecutive patients with cervical cancer, FIGO stages IB–IIB, were treated with combined external beam radiotherapy (EBRT), weekly concomitant cisplatin (40 mg/m2) and MRI guided HDR BT, from May 2011 until December 2012. EBRT consisted of IMRT (intensity modulated radiation therapy) to a physical dose of 45 Gy delivered in 1.8 Gy fractions. BT consisted of two applications (with a one-week interval) each comprising two HDR fractions, delivered in consecutive days (four BT fractions of 7 Gy, Supplementary Fig. 1). Applicator insertion (Utrecht tandem–ovoid applicator, Elekta Brachytherapy, The Netherlands) was performed under spinal-epidural anaesthesia [5]. Urinary and rectal catheters were inserted to control bladder and rectum filling, ensuring an empty bladder and rectum without gas. MR-imaging was performed according to the GEC ESTRO guidelines [6].

Contouring, dose parameters, image registration

MR-images were acquired after the applicator was inserted. A high-risk clinical target volume (HR-CTV) and the OARs (bladder, rectum, and sigmoid) were then contoured, and treatment plans were generated in the treatment planning system (Oncentra®, Elekta Brachytherapy, The Netherlands) [7]. The D90 HR-CTV (minimum dose to 90% of the HR-CTV) and D_{2cc} (minimum dose of the most exposed 2 cm^3 volume) of the OARs were calculated [8]. Physical doses were converted to EQD2 using the linear quadratic model with $\alpha/\beta = 10$ Gy for HR-CTV and $\alpha/\beta = 3$ Gy for OARs [9]. The planning objective for the HR-CTV was D90 $\geqslant$ 85 Gy EQD2 (total dose EBRT + BT). The constraints for the D_{2cc} OARs were 90 Gy EQD2 for the bladder and 75 Gy EQD2 for rectum and sigmoid. A detailed description of our treatment planning procedure is provided in a previous publication [5].

* Corresponding author. Address: University Medical Centre Utrecht, Department of Radiation Oncology, HP Q00.118, P.O. Box 85500, 3508GA Utrecht, The Netherlands.
E-mail address: c.nomden@umcutrecht.nl (C.N. Nomden).

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MR-images were acquired directly after insertion of the applicator (MRplan), prior to HDR irradiation (MRpre-irrad), and directly after the first fraction of each application (MRpost-irrad) (Supplementary Fig. 1). Re-calculation of the dose to the HR-CTV and OARs at different time points during BT was performed according to the following procedure (Supplementary Fig. 2):

(1) Pairs of scans were registered, relative to the applicator ((MRplan and MRpre-irrad) and (MRplan and MRpost-irrad)).
(2) The original contours of MRplan were re-sampled on MRpre-/MRpost-irrad.
(3) The contours were adapted according to the anatomy visible on the MRpre-/MRpost-irrad.
(4) The adapted contours were re-sampled on MRplan.
(5) $D90$ HR-CTV and D_{2cc} OARs values of the adapted contours were determined and converted to EQD2.

A single experienced observer reviewed all contours to reduce inter-observer contouring variation.

Organ displacement analyses

The $D90$ HR-CTV and D_{2cc} OARs values for the three time points were recorded, at MRplan, MRpre-irrad and MRpost-irrad. The dosimetric differences (ΔD) between pairs of time points were calculated for the following time intervals:

$$\Delta D\text{planning} = D\,(\text{MRpre-irrad}) - D\,(\text{MRplan}),\quad n = 30 \text{ fractions}$$

$$\Delta D\text{irradiation} = D\,(\text{MRpost-irrad}) - D\,(\text{MRpre-irrad}),\quad n = 26 \text{ fractions}$$

$$\Delta D\text{day} = D\,(\text{MRpre-irrad}_{\text{day2}}) - D\,(\text{MRplan}),\quad n = 30 \text{ fractions}$$

The means and standard deviation (SD) of the dose differences over each time interval were compared.

We calculated the total planned and the total estimated dose for each patient:

$$\text{Total planned dose} = D\,(\text{EBRT}) + 2 \times D\,(\text{MRplan BT1}) + 2 \times D\,(\text{MRplan BT3})$$

$$\text{Total estimated dose} = D\,(\text{EBRT}) + D\,(\text{MRpre-irrad BT1}) + D\,(\text{MRpre-irrad BT2}) + D\,(\text{MRpre-irrad BT3}) + D\,(\text{MRpre-irrad BT4}).$$

HDR and PDR comparison

Dose differences in the planning interval (ΔDplanning) and the day interval (ΔDday) for the 15 HDR patients ($n = 30$, $n = 30$ fractions) were compared with the doses of 10 patients treated with MRI guided PDR BT in 2011. These patients each received 2 PDR applications with a one week interval. Five patients had an additional MRI approximately four hours after MRplan ($n = 10$ fractions) and another five had an additional MRI on the second day of treatment ($n = 10$ fractions). Dose differences for both intervals, which are comparable to planning intervals and day intervals of HDR treatments, were compared as percentages of physical dose.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics software version 20. The dose differences calculated over the time intervals (except those with MRpost-irrad) were compared and tested for significance using the paired samples T-test. The Wilcoxon Signed Rank Test was used to analyse dose differences for intervals including the MRpost-irrad, as well as to compare HDR and PDR treatments. A p-value of <0.05 was considered significant.

Results/discussion

The average duration of the planning, irradiation, and day intervals was 3.9 (range 2.8–5.5) hours, 50 (range 37–74) minutes, and 23.1 (range 22.1–24.1) hours, respectively. On average, the dose differences calculated for the time intervals were small. The mean and standard deviation of the dose differences for HR-CTV and OARs are presented per fraction and per patient in Table 1. Overall, no significant dose differences were found between the different intervals. However, large, incidental differences were discovered in certain cases. For the rectum, differences up to 6 Gy EQD2 were found for individual fractions, with differences up to 10.2 Gy EQD2 for a single patient (Table 1 and Supplementary Fig. 3). These outliers in rectal dose are comparable to those described by Anderson et al. [3] for an interval of 5 h. Nesvacil et al. [1] analysed the variation in dose due to changing anatomy for several time intervals in 6 centres. Their mean intra-application variation and standard deviation for the rectal D_{2cc} was 3.8 (SD 20.5)%, and is consistent with our ΔDplanning and ΔDday values of 3.1 (SD 27.2) and 7.8 (SD 16)%, respectively. Lang et al. [2] showed similar, small, mean variation for the OARs, even for an interval of up to 20 h, which is comparable with our day interval (23 h). Furthermore, according to Mohamed et al. [10], applications after a time interval of one week result in similar small variations to the rectal D_{2cc}, namely 0.2 (SD 2.5) Gy EQD2 per fraction. The studies discussed show quite comparable systemic and random uncertainties for dose variations to the bladder, rectum, and sigmoid volumes, despite using different applicators, bladder filling protocols and types of afterloader.

In the present study, mean dose differences of −0.1–0.2 Gy EQD2, with standard deviations of 0.5–0.7 Gy EDQ2, were calculated for the HR-CTV (Table 1). These values are considered negligible compared to the contouring uncertainties of 9% presented by Hellebust et al. [11].

In this study, the dose variations for the OARs in the irradiation time interval (irradiation and re-imaging) were smaller than measured for the planning or the day interval (Table 1 and Supplementary Fig. 3). Given these small differences, MR-imaging after HDR dose delivery is not considered meaningful for dose calculations in clinical practice. It is worthwhile to realize, however, that these uncertainties persist, even for very short time intervals.

For the 10 patients treated with PDR, dose differences for HR-CTV were small for both planning and day intervals, and comparable with the differences observed for HDR treatments (Fig. 1). However, in the PDR group, larger mean dose differences were calculated for the OARs. Especially in the case of the rectum, the mean dose was found to increase significantly over time ($p = 0.037$), a phenomenon less obvious and not significant in HDR patients ($p = 0.178$) (Fig. 1). During PDR treatment, control of the rectal position is more difficult to achieve than for HDR treatments. Imaging prior to irradiation helps to identify unfavourable rectal movement, as well as volume changes such as passing gas. In these cases, insertion or adjustment of rectal catheters can help to stabilize the anatomical position and thereby the resulting rectal dose distribution. The MRpre-irradiation scanning procedure started with a short sagittal sequence, to be able to detect unfavourable changes in rectal anatomy. In 6 HDR fractions (4 patients), a rectal catheter was inserted or adjusted to have a rectal situation comparable to that of MRplan. The dose variations would have been larger for these patients if the interventions were not made. This may explain why the rectal dose differences calculated for the HDR groups are significantly lower than that of the PDR group (Fig. 1).