Original Research Article

Dosimetric impact of target definition in brachytherapy for cervical cancer – Computed tomography and trans rectal ultrasound versus magnetic resonance imaging

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ARTICLE INFO

ABSTRACT

Background and Purpose: Magnetic Resonance Imaging (MRI) based target definition in cervix brachytherapy is limited by its availability, logistics and financial implications, therefore, use of computed tomography (CT) and Trans Rectal UltraSonography (TRUS) has been explored. The current study evaluated the dosimetric impact of CT + TRUS based target volumes as compared to gold standard MRI.

Methods and Materials: Images of patients (n = 21) who underwent TRUS followed by MRI and CT, were delineated with High-Risk Clinical Target Volume in CT (CTV_{HR-CT}) and in MRI (CTV_{HR-MR}). CTV_{HR-CT} was drawn on CT images with TRUS assistance. For each patient, two treatment plans were made, on MRI and CT, followed by fusion and transfer of CTV_{HR-MR} to the CT images, referred as $CTV_{HR-MRonCT}$. The agreement between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} was evaluated for dosimetric parameters (D_{90}, D_{98} and D_{50}; Dose received by 90%, 98% and 50% of the volumes) using Bland-Altman plots, linear regression, and Pearson correlation.

Results: No statistically significant systematic difference was found between MRI and CT. Mean difference (± 1.96 SD) of D_{90}, D_{98} and D_{50} between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} was 2.0, 1.2 and 5.6 Gy respectively. The number of patients who have met the dose constraints of $D_{90} > 85$ Gy were 90% and 80% in MR and in CT respectively, others were in the borderline, with a minimum dose of 80 Gy. The mean $\pm$ SD dose-difference between MR and CT plans for bladder was significant (5 $\pm$ 13 Gy; p = 0.12) for $D_{0.1cm3}$, while others were statistically insignificant.

Conclusion: CT + TRUS based delineation of CTV_{HR} appear promising, provide useful information to optimally utilize for brachytherapy planning, however, MRI remains the gold standard.

1. Introduction

Three-dimensional image guided adaptive brachytherapy (3D-IGABT) using magnetic resonance imaging (MRI) is associated with improved local control and reduced toxicities [1–4]. Although MRI is superior for target definition, its wide applicability is limited by its availability, logistics and financial implications [5]. Hence, use of alternate imaging modalities including computed tomography (CT) or Ultrasound (US) had been explored [5–13]. Utilization of CT is generally higher as compared to MRI for Brachytherapy (BT) planning of cervical

cancer [14,15]. In the recent past, attempts to define targets on CT have been reported with over-estimation in width towards the parametrium and underestimation in height towards the uterus [5–9]. It has also been reported that Trans-Rectal Ultrasound (TRUS) is beneficial for the delineation of target structures at the time of BT, with smaller and acceptable deviations as compared to MRI [6–8,12–13].

We recently reported on defining the target on CT incorporating intra-operative TRUS findings related to primary tumor at cervix at the time of BT in a prospective study. The major finding of that study was that the CT based target incorporating real time TRUS information was comparable to the gold standard MRI at the time of BT [16]. As a next logical step, validation of treatment planning and dosimetric performance of this approach was undertaken. The current study evaluated clinically relevant dosimetric impact of CT + TRUS based target volumes as compared to gold standard MRI based target volumes during BT using dose - volume parameters as recommended by ICRU 89 [17].

2. Materials & methods

2.1. Patient Characteristics, imaging and contouring

Images of patients (n = 21) with histologically proven cervical cancer, enrolled in the EMBRACE-I study (European study on MRI-guided BRAchytherapy in locally advanced CErvical cancer) from our institution were included. The current study was approved by the institutional ethics committee and patients were consented for participation. The details of patient characteristics, External Beam Radiotherapy (EBRT) and BT have been reported [4]. In brief, all patients had curative treatment consisting of EBRT with or without concurrent chemotherapy and MR IGABT [4,16,18]. MR images (1.5 Tesla Signa Horizon GE Medical systems, Milwaukee WI) consisted of T1, T2, axial, sagittal and coronal sequences of 256×256 matrix and 3–4 mm slice thickness with 0–1 mm gap [4,16,18]. As part of the prospective study, patients during BT application underwent real time TRUS (Transrectal biplanar probe, 5–7 MHz crystal, Esaote's MyLab 50) in sagittal longitudinal and transverse orientation, at various levels of cervical canal with 1 cm step size.

CT images were acquired with a defined protocol including bladder filling and intra-venous contrast, which were transferred to the Treatment Planning System (TPS) (Oncentra Masterplan® V4.1, Nucletron, Elekta AB, Stockholm, Sweden). Image registration between CT and TRUS images were not carried out, due to various reasons which include poor visualization of the applicator geometry in the US, difference in the image orientation between MRI and US, inadequate tools in the TPS among others. Therefore, the delineation of high-risk CTV (CTV$_{HR-CT}$) on CT images was carried out manually with the help of TRUS images, where the US images were placed on a second monitor beside the TPS. Detailed comparison of CTV$_{HR-CT}$ with MR based (CTV$_{HR-MR}$) volumes has been reported recently [16]. Organs at risks (OARs) consisting of bladder$_{CT}$, rectum$_{CT}$ and sigmoid$_{CT}$ were delineated on CT images. Gross tumor volume at BT (GTV$_{MR}$), CTV$_{HR-MR}$, Intermediate-risk clinical target volume (CTV$_{IR-MR}$) and OARs (bladder$_{MR}$, rectum$_{MR}$ and sigmoid$_{MR}$) were contoured on MR images [19].

2.2. Treatment planning

For each patient, two treatment plans were created: a) Clinical plan using MR images only (MR plan). b) A new treatment plan using CT images (CT plan).

2.2.1. MR plan

Applicator reconstruction was done, followed by the definition of ICRU dose points [17]. Institutional standard loading pattern was used to load the tandem and the ring with point-A normalized to 7 Gy per fraction [20]. Target coverage and dose to OARs were evaluated and optimized manually. If the target coverage was inadequate, source

positions in the needles were loaded based on the CTV$_{HR-MR}$. Individual dwell times in the needles were loaded approximately to 15–20% of the intra-cavitary component, followed by manual/graphical optimization as required to meet the planning aims [17]. Treatment planning was simulated for four High Dose Rate (HDR) fractions using the planning aims combining EBRT and total BT dose: CTV$_{HR-MR}$ D$_{90}$ (Dose received by 90% of the CTV$_{HR-MR}$) of 85 Gy EQD2$_{\alpha/\beta=10}$, and OAR D$_{2cm3}$ (Minimum dose received by the most exposed 2 cm^3 volume of the OAR) of 90 Gy EQD2$_{\alpha/\beta=3}$ for bladder and 70 Gy EQD2$_{\alpha/\beta=3}$ for rectum and sigmoid. This plan was used for clinical purposes.

2.2.2. CT plan

A new treatment plan was created using CT images, where the planner was blinded to dose-volume parameters of MR plan. However, the same methodology of MR planning was used to generate the CT plan. Dose to CTV$_{HR-CT}$ and OARs including bladder$_{CT}$, rectum$_{CT}$ and sigmoid$_{CT}$ were evaluated for the planning aims as described in the previous section, to arrive at an optimal plan, which would be clinically acceptable. This plan was used for this dosimetric study only.

2.3. Image registration between MR and CT images

To evaluate the dosimetric impact of CTV$_{HR-CT}$ as compared to gold standard CTV$_{HR-MR}$, CT and MR images at the time BT were fused based on the applicator using landmark rigid registration (Fig. 1a). The registration was based on well-defined points which could be visualized well both in CT and MRI. The points were on the applicator, such as, tip of the tandem, ring centre and the needles. The registration was followed by the transfer of CTV$_{HR-MR}$ to the CT images [21,22] (Fig. 1b). CTV$_{HR-MR}$ when transferred to CT images was referred as CTV$_{HR-MRonCT}$. The dose received by CTV$_{HR-MRonCT}$ in CT plan, is an estimate of the dose received by the gold standard CTV$_{HR-MR}$ in CT + TRUS environment. The transfer of CTV$_{HR-MR}$ to the CT images resulted in the estimation of the dose received by the CTV$_{HR-MR}$ which is considered as a ground truth in a CT-only environment. OARs were not transferred from MR to CT.

The CT plans were created by a single experienced Medical Physicist (JS); however, the image registration was performed (PA) and double checked by a second (JS) or a third physicist (JJ). MRI clinical plans were performed by a single experienced Medical Physicist (JS), however, multiple Physicists did second check before the plan was approved for treatment in compliance with the departmental protocol.

2.4. Analysis

Pearson correlation was used to compare volumes of CTV$_{HR-MR}$ and CTV$_{HR-CT}$. The agreement between the dosimetric parameters (D$_{90}$: Dose received by 98% of the volume, D$_{98}$: Dose received by 98% of the volume, D$_{50}$: Dose received by 50% of the volume) of CTV$_{HR-MRonCT}$ vs CTV$_{HR-CT}$ were evaluated based on Bland-Altman plots. In addition, Total Reference Air Kerma (TRAK) and dose received by point-A were compared between the plans. Linear regression analysis was used to evaluate the relation between the volume and the dose difference between CT and MR dosimetric parameters. Quantitative comparison of the dose-volume parameters was carried out using the standard two-tailed paired *t*-test (for normally distributed data), and Wilcoxon signed rank test (for non-normal data). All differences were reported with 95% confidence interval. The threshold for statistical significance was p $\leq$ 0.05.

Although only one BT fraction was used for the current analysis, to enable comparison of the dose-volume parameters with the existing clinical evidence in MR IGABT, dose from single BT fraction was extrapolated to include EBRT and total BT in EQD2.

All patients were treated using HDR Iridium − 192 (MicroSelectron) using the MR plan. The dose calculation algorithm was TG 43 [23].
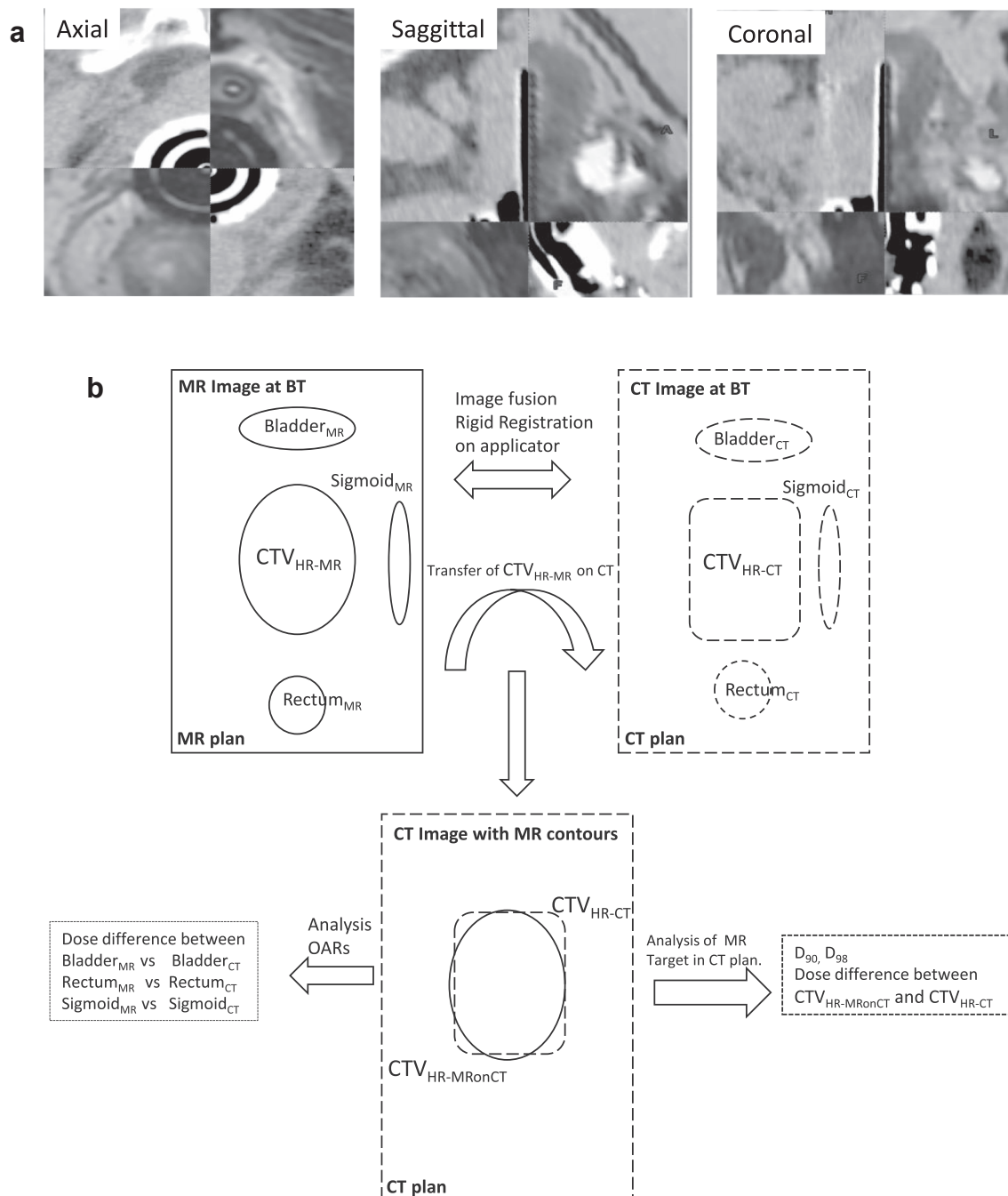
Fig. 1. (a) A representative image depicting the image-registration between CT and MR using landmark rigid registration based on applicator. (b) Schematic representation of the methodology for the evaluation of dosimetric impact of CT and TRUS based delineation as compared to gold standard MRI.

3. Results

The mean $\pm$ standard deviation (SD) volume of CTV$_{HR}$ was 35 ± 14 cm^3 for MR and CT + TRUS volumes with a Pearson's correlation coefficient of 0.9, suggesting a strong correlation
($p < 0.001$). A representative patient is presented in Fig. 2, depicting the spatial location of the CTV$_{HR-MR}$ and CTV$_{HR-CT}$.

In the current cohort, 18/21 patients had intracavitary + interstitial (IC + IS) application, with additional needles in the parametrium, while 3/21 had intracavitary (IC) application. Mean $\pm$ SD errors of image registration accuracy between CT and MR anchor points were 1.1 ± 0.03 mm in lateral, 1.2 ± 0.05 mm in superior-inferior and 1.2 ± 0.06 mm in anterio-posterior direction (Fig. 1a).

3.1. Dose to CTV$_{HR}$

No statistically significant systematic difference in the dosimetric parameters was found between MR and CT plans for target structures (Table 1). Mean dose difference (± 1.96 SD) between CTV$_{HR-MRonCT}$ and CTV$_{HR-CT}$ was observed as 2.0 Gy$_{\alpha/\beta=10}$ for D$_{90}$, 1.2 Gy$_{\alpha/\beta=10}$ for D$_{98}$ and 5.6 Gy$_{\alpha/\beta=10}$ for D$_{50}$ (Figs. 3a-b). Although the mean dose-differences were small in magnitude, the limits of agreement were high (2 SD), ranged from -17 to 21 Gy$_{\alpha/\beta=10}$ for D$_{90}$ and -18 to 20 Gy$_{\alpha/\beta=10}$ for D$_{98}$. The wider dose difference may be attributed to the four outliers; however, the range becomes narrower to 5–13 Gy$_{\alpha/\beta=10}$ by excluding them. It was also observed that, for 19/21 (90%), and 20/21 (95%) patients, the limits of agreement were within 2 SD, for D$_{90}$ and D$_{98}$ respectively (Figs. 3a-b, Table 1).
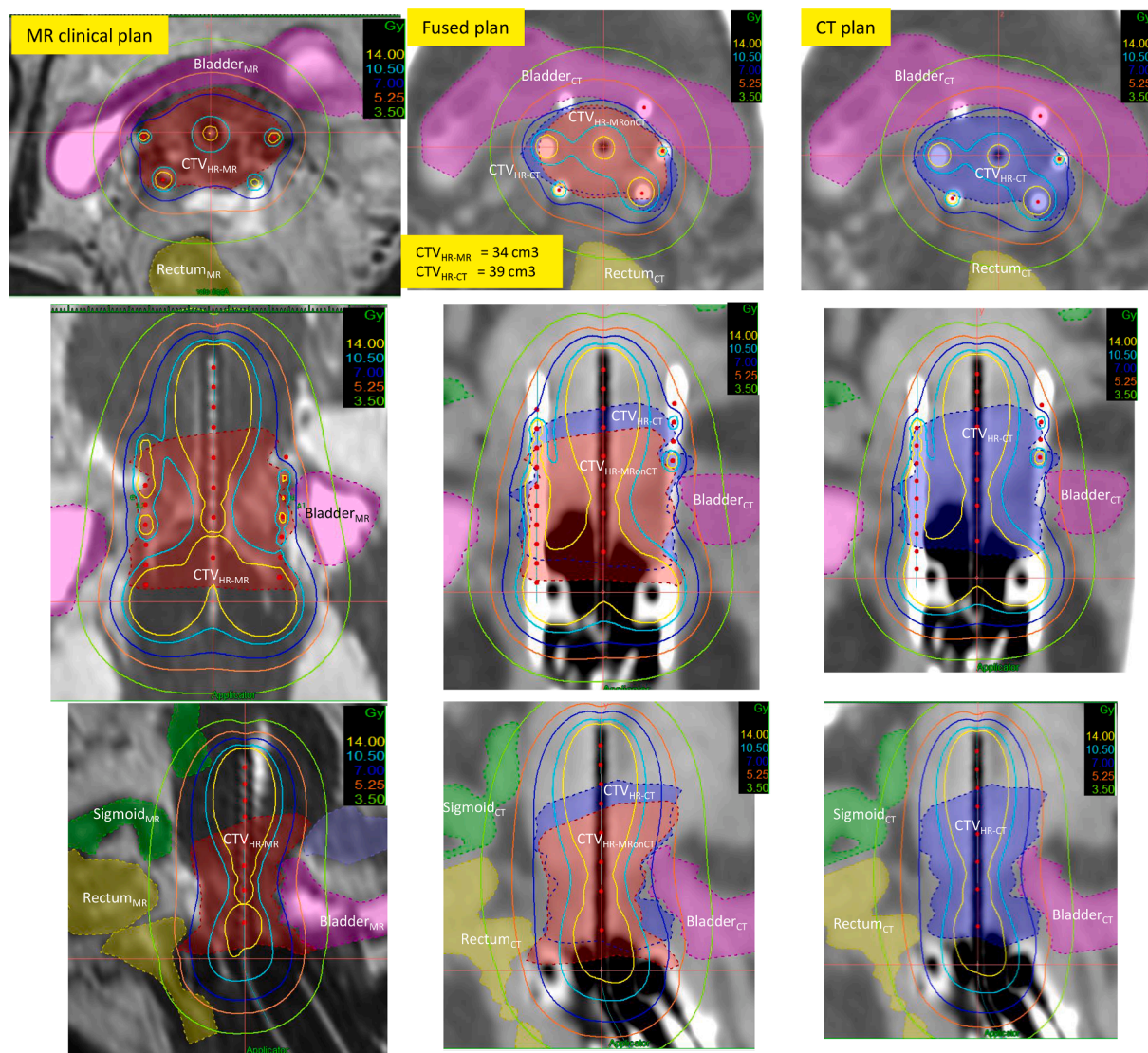
Fig. 2. A representative image of a patient of all the three plans. This example case is a stage IIIB tumor with medial parametrium extension at BT. The volume CTV_{HR} was 34 cm^3 in MR and 39 cm^3 in CT. 1st, 2nd and 3rd row show transverse, coronal and sagittal orientation of a combined IC + IS applicator in situ. 1st column is the clinical MR plan. 2nd column is the CT plan with MRI and CT contours, and 3rd column CT plan.

The dose-differences were found in D_{90}, between $CTV_{HR-MRonCT}$ and CTV_{HR-CT}, to be scattered around the origin (bias-line), but with a specific trend, where it was observed that for 14/21 (65%) patients, the dose to $CTV_{HR-MRonCT}$ was higher than CTV_{HR-CT}. For the other patients, 7/21 (35%), the dose received by CTV_{HR-CT} was higher than $CTV_{HR-MRonCT}$ (Fig. 3a). Similar findings were also found for D_{98} (Fig. 3b).

The percentage of patients who have met the dose constraints of D_{90} > 85 $Gy_{\alpha/\beta=10}$ was 90% (19/21) in MR and 80% (17/21) in CT plans. The rest of the patients, 20% (4/21) in CT, were in the borderline, and received at least a minimum dose of 80 $Gy_{\alpha/\beta=10}$ (Fig. 4a).

In the current cohort, most of the patients (60%) had large volume of CTV_{HR-MR}, (>30 cm^3, mean ± SD 43 ± 12 cm^3, range: 30–68 cm^3) at the time of BT, while 14% of patients had intermediate volumes (25–29 cm^3), rest of the 24% patients had small volumes of CTV_{HR} (<25 cm^3). The maximum dose-difference was observed for five patients, in various volume levels of CTV_{HR-MR} (17 cm^3, 19 $Gy_{\alpha/\beta=10}$; 30 cm^3, 13 $Gy_{\alpha/\beta=10}$; 38 cm^3, −18 $Gy_{\alpha/\beta=10}$; 43 cm^3,-19 $Gy_{\alpha/\beta=10}$ and 68 cm^3,-15 $Gy_{\alpha/\beta=10}$), while others have resulted in a dose-difference of ± 10 $Gy_{\alpha/\beta=10}$, suggesting that there is no correlation of dose-difference to the size of CTV_{HR-MR} volumes (Fig. 4b).

The investigation of the dose-differences (D_{90}) between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} in relation to the volume-difference between CTV_{HR-MR} and CTV_{HR-CT} revealed that the rate of change of dose with respect to volume was −1 $Gy_{\alpha/\beta=10}$/cm^3 (slope of the curve) meaning that, for every 1 cm^3 of additional volume in CT + TRUS, the dose to $CTV_{HR-MRonCT}$ was higher by an average of 1 $Gy_{\alpha/\beta=10}$ (Fig. 4c). However, the mean dose received by $CTV_{HR-MRonCT}$ was higher by 2.6 $Gy_{\alpha/\beta=10}$ (y intercept- Fig. 4c, R2 = 0.7), as compared to CTV_{HR-CT}, due to the overestimated volumes of CTV_{HR-CT} in 12/21 (60%) patients.

3.2. Organs at risk (OAR)

The mean ± SD dose-difference between MR and CT plans for bladder was 5 ± 13 $Gy_{\alpha/\beta=3}$ for $D_{0.1cm3}$. For other organs, rectum and sigmoid, the dose-difference was found to be less than ± 3 $Gy_{\alpha/\beta=3}$ between MR and CT plan, and not statistically significant (Table 1).

3.3. TRAK, loading pattern and point A

TRAK was marginally more in CT plan as compared to MR (0.44 ± 0.04 vs 0.43 ± 0.07 cGy at 1 m; p = 0.48), but not statistically significant as other parameters (Table 1).

Table 1

Mean ± SD dose in EQD2 to CTV$_{HR}$ for MR plan, MR contour on CT plan and CT plan. Mean ± SD values of dose volume parameter of organs at risk, Total Reference Air Kerma (TRAK), and loading pattern for MR and CT plan. Parameters in bold represent statistically significant difference between MR and CT plan.

Organ	Dose parameter [unit]	MR plan	MR contour on CT plan	CT plan	p value "MR contour on CT plan" vs CT Plan.
CTV$_{HR}$	D$_{90}$ [Gy]	90 ± 4	91 ± 8	89 ± 6	n.s.
	D$_{98}$ [Gy]	81 ± 5	79 ± 8	78 ± 6	0.076
	D$_{50}$ [Gy]	126 ± 11	129 ± 14	124 ± 11	n.s.
Bladder	Volume [cm^3]	89 ± 31	----	79 ± 30	
	D$_{2cm3}$ [Gy]	84 ± 5	----	80 ± 6	0.083
	D$_{0.1cm3}$ [Gy]	104 ± 11	----	98 ± 8	**0.012**
	ICRU Point [Gy]	71 ± 16	----	68 ± 11	n.s
Rectum	Volume [cm^3]	39 ± 11	----	41 ± 24	
	D$_{2cm3}$ [Gy]	63 ± 5	----	64 ± 5	0.166
	D$_{0.1cm3}$ [Gy]	74 ± 9	----	78 ± 11	0.101
	ICRU RV Point [Gy]	66 ± 7	----	65 ± 5	n.s.
Sigmoid	Volume [cm^3]	35 ± 20	----	41 ± 28	
	D$_{2cm3}$ [Gy]	66 ± 7	----	68 ± 5	n.s
	D$_{0.1cm3}$ [Gy]	82 ± 13	----	82 ± 8	n.s.
TRAK [cGy at 1 m]	Total TRAK	0.43 ± 0.07	---	0.44 ± 0.04	n.s.
	Intra Uterine TRAK	0.19 ± 0.05	----	0.19 ± 0.03	n.s.
	Vaginal TRAK	0.20 ± 0.05	----	0.21 ± 0.03	n.s.
	Interstitial needle TRAK	0.04 ± 0.03	---	0.042 ± 0.03	n.s.
Loading Pattern	Needle loading/(Tandem + vaginal) %	11.3 ± 9	---	11.1 ± 8.5	n.s.
	Vaginal loading/tandem loading %	114 ± 32	----	114 ± 25	n.s
Point A *	= (14 * TRAK) [Gy]	78 ± 9	----	79 ± 7	n.s.

4. Discussion

The current study evaluated clinically relevant dosimetric impact of CT + TRUS based target volumes as compared to gold standard MRI based target volumes. No significant systematic differences in dose-volume parameters for target and OARs were observed.

The clinical paper on the same patient cohort, reported a significant correlation (p < 0.001) of CTV$_{HR-MR}$ and CTV$_{HR-CT}$ dimensions (width and thickness) at various levels, with a mean difference in width of 1–4 mm, irrespective of parametrial involvement [16]. Although both the patient cohorts were the same, four patients were excluded from the current study, as image registration was not successful in these patients, which may be attributed to the difference in the slice thickness, orientation, and inadequate tools in the TPS.

The volume of CTV$_{HR-CT}$ was on average slightly overestimated, which resulted in slightly higher average dose to CTV$_{HR-MRonCT}$ as compared to MR plan. A previous inter-observer study in MRI found an average discrepancy (SD) between observers of 5.5 Gy$_{\alpha/\beta=10}$ [24]. Therefore, a significant fraction of the discrepancy between MRI and CT based contouring demonstrated in this study (SD of 8.6 Gy$_{\alpha/\beta=10}$) may likely be related to the intra-observer uncertainties that were observed in MRI as well. Furthermore, the dose discrepancy in the current study is also affected by image registration uncertainties, which was not present in Hellebust et al [24]. Upon investigating the individual patients and outliers, for volume and dose-difference various observations were made. When the volume-difference between CTV$_{HR-MR}$ and CTV$_{HR-CT}$ was spatially at the lateral extension of the tumor towards parametrium, the dose-difference was the largest, due to the steep dose gradients and needle loading (Fig. 5a). However, when the volume-difference was more superior above the level of point-A, the dose-difference was modest, which may be attributed to the clinical practice. In the current clinical practice, the tandem loading was not conformed to the CTV$_{HR}$ superiorly, but always loaded from the tip of the tandem. This may not be true when the loading pattern conforms to the CTV$_{HR}$ (Fig. 5b). Another outlier was when the volume variation is located spatially at the superior level near the fundus, for large volume tumors, the dose-difference was large due to the high - dose gradient in this region (Fig. 5c).

It has been reported that a CTV$_{HR}$ dose of ≥ 85 Gy$_{\alpha/\beta=10}$ (D$_{90}$) delivered in 50 days, provided 3-year local control rates of more than 93% in intermediate size (30 cm^3) CTV$_{HR}$ [25]. It must also be noted that the large mono-institutional series with application of MRI based IGABT

have confirmed high levels of local control (>90%) at mean CTV$_{HR}$ doses around 90 Gy$_{\alpha/\beta=10}$ [26–30] for combined IC + IS applicators for CTV$_{HR}$ volumes ≥ 30 cm^3 [26]. Hence, dose to CTV$_{HR}$ is very important. In the current study, majority of the patients (90%), met the threshold dose of D$_{90}$ > 85 Gy$_{\alpha/\beta=10}$ in MR, while in CT it was only 80%. The rest of the 20% (4/21) of the patients in CT, were in the borderline, receiving a dose more than 80 Gy$_{\alpha/\beta=10}$. Considering the overestimation of CTV$_{HR}$ volumes, it may be acceptable to have smaller fractions of patients adhering to 85 Gy$_{\alpha/\beta=10}$ dose constraint in CT + TRUS environment as compared to an MR-only environment. CTV$_{HR}$ D$_{98}$ represents the spatial dose distribution within and at borders of the target volumes. This DVH parameter is relevant for plan evaluation and the detection of low dose regions not reflected in D$_{90}$ [31]. Although the dose to CTV$_{HR-CT}$ was systematically smaller by 1 ± 10 Gy$_{\alpha/\beta=10}$, as compared to CTV$_{HR-MR}$, the number of patients not meeting the constraint may be attributed to the contouring uncertainties inherent to D$_{98}$ [31]. The current methodology of delineation of CTV$_{HR}$ may be safe to adopt, with respect to the threshold doses established for MR IGABT.

Bladder dose resulted in large variation between MR and CT plan, while rectum and sigmoid did not show any significant difference, which may be attributed to the inconsistent bladder volume at the time of imaging of MR and CT, as compared to rectum, which was more stable. In general, visualization of OARs was superior in MRI as compared to CT. In the current study, the visualization of OARs in CT, especially bladder and bladder wall were superior. This was possible due to the contrast material inserted in the bladder during imaging, and the applicator material, which was made of polymer, resulted in less or no artifacts. This concept may be validated for applicator materials made up of titanium and other materials for CT based planning.

TRAK was consistent between MR and CT plans, which may be attributed to the standard treatment planning principles followed between the two approaches, which reiterate the robustness of the planning. Point A* dose was more than 78 Gy$_{\alpha/\beta=10}$ in both MR and CT plans. Point A* correlates with 75 Gy$_{\alpha/\beta=10}$ and 85 Gy$_{\alpha/\beta=10}$ iso-dose surface volumes, which indicates that the dose planning resulted in similar size of irradiated volume for MR and CT based planning [32]. Since a sizable number of our patients still undergo, 2D image-based BT planning based on orthogonal radiographs and point-A normalization, it is important for the department protocol, to keep a track of point-A, in CT planning for population-based dose comparison, not only for IC but also for IC + IS implants.

It was previously reported that TRUS in combination with CT,
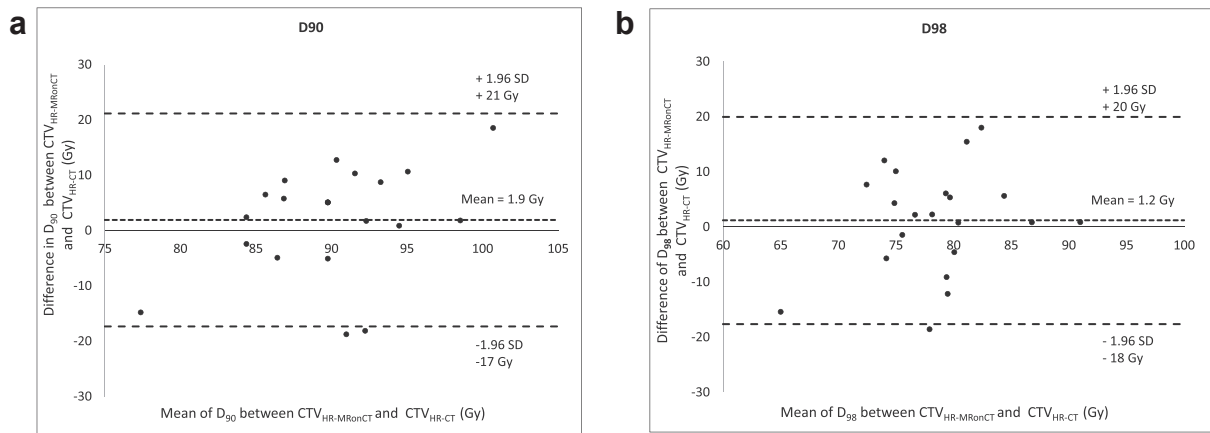
Fig. 3. (a) Mean D_{90} vs Dose difference in D_{90} between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} – (Bland-Altman plot). The mean dose-difference was 1.9 Gy, the limits of agreement (2 SD), ranged from −17 to 21 $Gy_{\alpha/\beta=10}$. (b) Mean D_{98} vs Dose difference in D_{98} between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} – (Bland-Altman plot). The mean dose-difference was 1.2 Gy, the limits of agreement (2 SD), ranged from −18 to 20 $Gy_{\alpha/\beta=10}$.
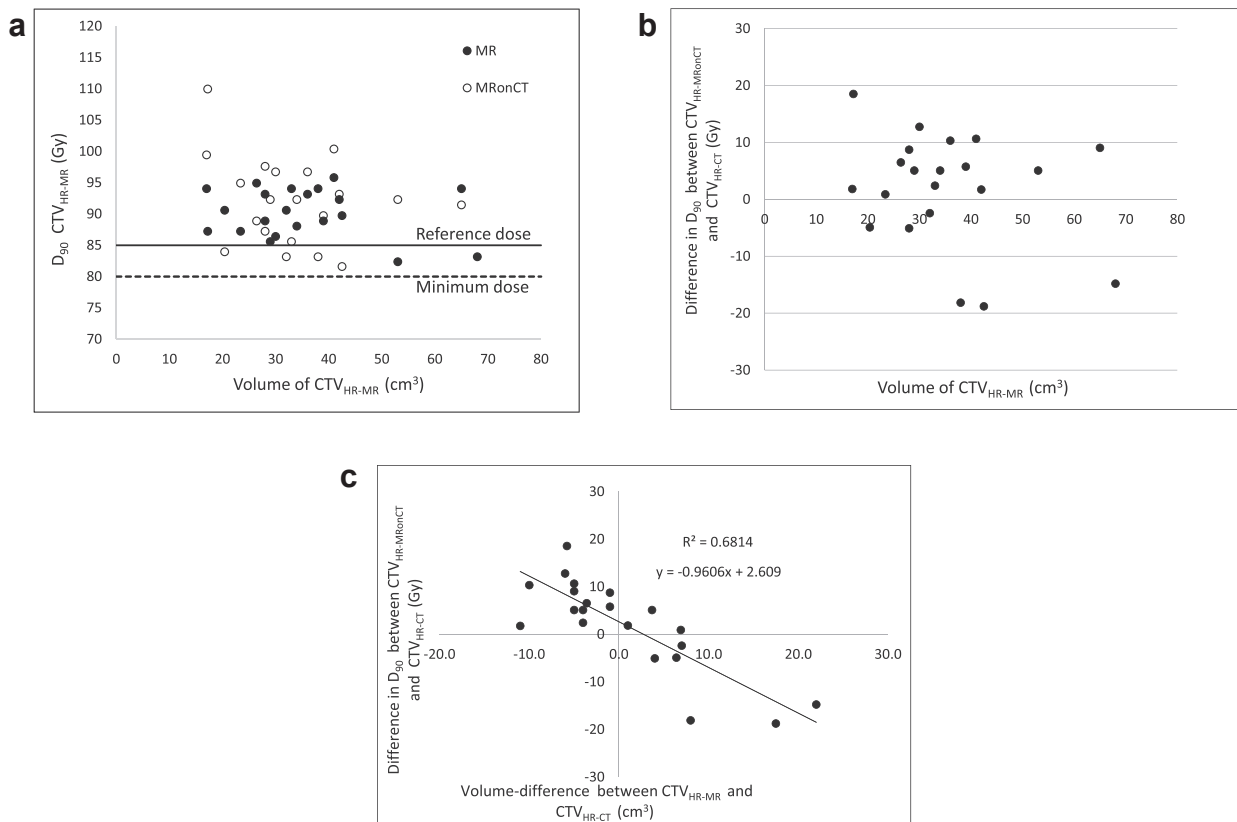
Fig. 4. (a) D_{90} of CTV_{HR-MR} as a function of volume for MR and MRonCT plans. The thick line and the dotted line represent the reference dose constraint of $D_{90} > 85$ $Gy_{\alpha/\beta=10}$ of MR plans, and the minimum dose 80 $Gy_{\alpha/\beta=10}$ in CT plans. (b) Difference in D_{90} between $CTV_{HR-MRonCT}$ and CTV_{HR-CT} as a function of volume of CTV_{HR-MR}. (c) Volume difference (CTV_{HR-MR} and CTV_{HR-CT}) as a function of dose difference in D_{90} ($CTV_{HR-MRonCT}$ and CTV_{HR-CT}).

provides excellent agreement as compared to MR, for the delineation of CTV_{HR}, and the current clinical paper on the same cohort agrees with other findings [33,16]. In another comparison between MR and CT delineation of CTV volumes, a high level of agreement was reported, which was attributed to the more distinct contrast medium visible on the images at the time of BT [11]. However, this was based on a limited number of patients with complete/partial response at the time of BT, while the current cohort involves large tumors with parametrial extension. Moreover, majority of the patients in the current study, had IC + IS applicator, and hence, it was possible to optimize the dose. However, these findings may not be applicable for simple IC applications, where

the degrees of freedom is less for dose optimization, leading to an inadequate target coverage.

The dosimetric parameters validated for MR IGABT, may be adopted for CT + TRUS based delineation of CTV_{HR-CT}, however, it must be noted that the current study was based in a well experienced MR IGABT clinic, where CTV_{HR-CT} was drawn on CT images utilizing additional guidance from TRUS performed during BT procedure by an expert with a sound knowledge of MR and TRUS/Trans-Abdominal US based IGABT [7–8]. There is a definite learning curve for the use of CT imaging with TRUS guidance even for experienced centers with MR IGABT. The current findings must be studied, with a larger cohort, spanning multiple clinical
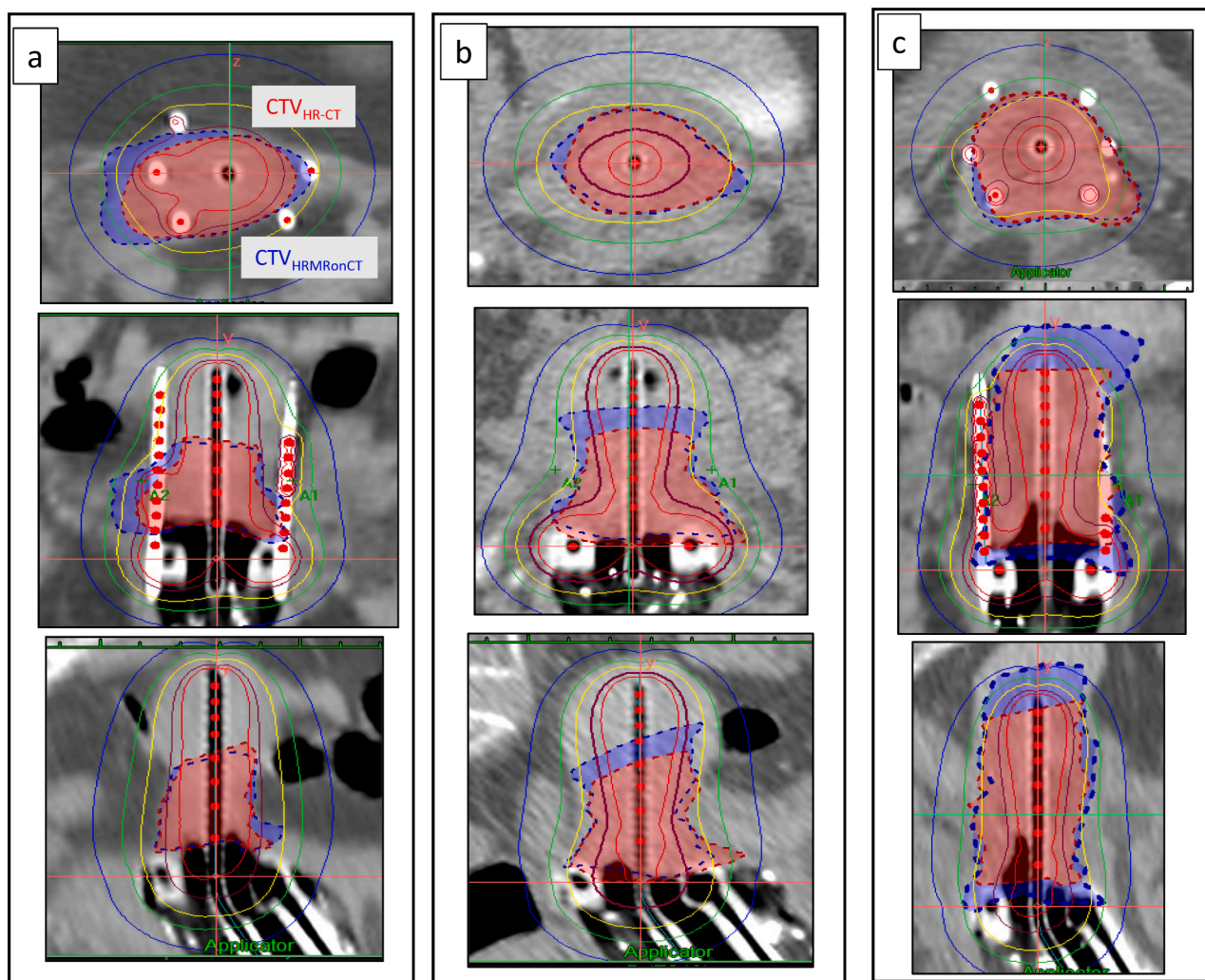
Fig. 5. Representative image of an outlier, where the spatial variation between CT + TRUS and MR contours was at the level of (a) the parametrium, impacting a large dose variation, due to the presence of interstitial needels. (b) Point - A, resulted in a modest dose variation. (c) Fundus, resulted in large dose variation.

users with various levels of experience in IGABT, to allow homogeneous dose adoption of CT + TRUS and MRI environments.

Dose-volume parameters reported in the current study were obtained for a single BT fraction, which was extrapolated to four BT fractions, mimicking the same dose for all fractions. Although this seems acceptable in most cases to a large extent, it may exclude inter application variations [34]. Contouring of GTV is not feasible on CT images, however, CTV_{IR} delineation is possible, but not delineated here, therefore, was not part of the current study. Although, the sample size was limited for documenting the overall performance of CT based DVH parameters in a representative patient cohort, for the purpose of evaluating the differences between MR and CT + TRUS, a sample size of 21 patients is acceptable. Prospective validation of these concepts on CT based IGABT is being planned in a multi centre trial setting in the future.

In conclusion, with the previous report of limited systematic differences in mean volumes and width of CTV_{HR} between gold standard MR as compared to CT + TRUS image-based delineation, the current dosimetric study suggests no significant systematic differences in dose-volume parameters for target and OARs. However, considerable variations were seen on individual patient level which needs to be considered during the clinical practice and needs further investigations. Although, CT + TRUS based delineation of CTV_{HR}, appear promising, MRI remains the gold standard. The findings of the current study provide useful information to optimally utilize various imaging modalities for BT planning.

5. Data availability statement

Data in the form of dose–volume parameters can be made available as supplementary material, but not the DICOM files due to our hospital data sharing policy.

6. Clinical trial information

The study is not a clinical trial, but patient data used in the current study were part of the clinical trial - EMBRACE - External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer (EMBRACE-I).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicole Nesvacil, Christian Kirisits and Max Schmid report no conflicts of interest for this study, however, they received funding outside the current study from Varian Medical Systems, Elekta Medicals and Christian Doppler laboratory for EMBRACE clinical trial. Supriya Chopra receives

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