

Research Article**Assessment of Organ Motion Impact on Brachytherapy Treatment Planning of Cervix Cancer**

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Abstract

Purpose: To quantify dosimetrically the impact of intra-fractional organs movements during brachytherapy treatment of cervix cancer (CC).

Material and Methods: Eight consented patients (a total of 12 fractions) undergoing CC brachytherapy underwent a second paraxial T2-weighted MRI (MRI2) about 2-3 hours after the initial planning MRI (MRI1) and before treatment delivery. The organs at risk (OARs) were delineated on MRI1/MRI2. MRI2 and MRI1 were rigidly registered. The high-risk clinical target volume (HR-CTV), the intermediate risk CTV (IR-CTV), and the dose map were copied from MRI1 to MRI2. Dose volume histogram (DVH) metrics were then calculated for the structures contoured on both scans, following the EMBRACE II guidelines. The minimum doses received by 90% and 98% of the HR-CTV or IR-CTV were computed as D90 and D98 respectively. The minimum doses received by the most exposed volumes of 0.1 cm³, 2 cm³, and 5 cm³ of the OARs were computed as D0.1cc, D2cc, and D5cc respectively. The percentage of DVH metric deviations (PDMD) from the reference DVH measurements on MRI1 were calculated. The average EQD2 per fraction was computed for the OARs and compared between MRI1 and MRI2.

Results: Dose deviations due to displacement and deformation were within 8% for OARs and 1% for CTVs. The highest PDMD, when considering standard deviation, was D98 = 1.02±1.54% for HR-CTV, D98 = 0.98±1% for IR-CTV, and D0.1cc = 5.4±20.49% for the rectum in the group of OARs. EQD2 did not change drastically between both MRI.

Conclusions: Re- imaging before dose-delivery demonstrated anatomical changes in the OARs during treatment compared to planning, and this was quantified dosimetrically. Special caution should be taken during planning when DVH metrics are close to

dose constraints.

Keywords: cervix cancer, brachytherapy, MRI scan, dosimetry, organs at risk, motion.

Purpose

Cervix cancer (CC) is the fourth most common cancer in women worldwide with an estimated total number of 604 127 cases and 341 831 deaths in 2020 (1). The standard approach for treating CC typically involves surgery, chemotherapy, and radiation therapy. Usually, external beam radiotherapy is followed by high dose rate (HDR) brachytherapy. In brachytherapy, the motion of the target with respect to the radiation source is negligible as the applicator is fixed to the cervix and follows its movement. However, the nearby organs at risk (OARs) are moving around the implant and due to their proximity to the treatment target and radiation sources, the dose calculations at their location significantly impact the treatment planning process. The dose is optimized based on the delineation of the OARs using planning MRI that are acquired while the applicator is inserted into the patient's cervix. Hence, the change in OAR positioning related to the applicator, variation of shape and/or filling between planning and treatment may impact the accuracy of the dose delivered.

Several studies have addressed the issue of intra-fractional(2-4) and inter-fractional(4,5) organs motion in brachytherapy. Intra-fractional organ motion refers to the movement/ deformation of organs within the body during a single radiation treatment session. This can affect the precise delivery of radiation to the intended target area. Inter-fractional organ motion in brachytherapy refers to the movement /deformation of organs within the body between different radiation treatment sessions or fractions. Managing and accounting for intra-fractional and inter-fractional organ motion is important in brachytherapy to ensure that the radiation dose is accurately delivered to the target and that nearby healthy tissues or organs are spared from excessive radiation exposure. Yan et al. (2) considered pre-delivery Cone Beam CT (CBCT) from which structures were delineated and doses recalculated and compared to those of the planning CT. Mazon et al. (3) assessed intra-fractional organs movement during the delivery of pulsed-dose-rate brachytherapy in cervical cancer. They performed three CT scans: one before the treatment delivery and after the post-implantation MRI (Day 1), and two during the treatment delivery (Days 2 and 3). Nes-

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vacil et al. (4) focused mainly on movements between planning scan acquisition and treatment delivery either between the application and the fraction (intra-application) or when applying a previous plan to a new application (inter-application). Patil et al. (5) evaluated inter-fractional organs and target movements based on the acquisition of CT image before each treatment delivery (fractions two, three and four) while MRI based planning was done for the first fraction only and used for the other fractions.

While inter-fractional organs movement is not an issue in HDR brachytherapy in our clinic as the patient is imaged before each fraction, intra-fractional organs movement could be problematic and needs to be assessed. In our clinic, HDR brachytherapy treatment of cervix cancer is planned based on MRI which is the gold standard (6) but to the best of our knowledge, the assessment of the intra-fractional organs motion was not done for this kind of MRI based procedure. The purpose of this study was to quantify dosimetrically the impact of intra-fractional organs motions. While the applicator is inserted in the cervix (intra-application), a first MRI was acquired for the planning of the treatment (2-3h before treatment) and a pre-delivery MRI was acquired just before treatment (~30min before). The dose received by the structures delineated on both MR sequences were compared.

Material and Methods

Patients and Treatment Description

This research was a hospital-based prospective study approved by the institutional ethics committee (number MRC-01-21-697) and all participating patients gave their written consent. Eight cervix cancer patients treated with chemoradiation between 2021 and 2023 were included. The TNM stages of the tumor were IIB, IVB, IIIB for 50%, 20%, 20% of patients respectively. The grades of the tumor were II for 40% of patients and III for 60% of patients. The histological type of the cancer was squamous cell carcinoma, small cell, adenocarcinoma for 63%, 25%, 12% of patients respectively.

All patients were treated with external beam radiotherapy of 45 Gy in 25 fractions for five weeks using Volumetric-Modulated Arc Therapy on the linear accelerator. This was along with weekly chemotherapy with cisplatin 40 mg/m2. Following these treatments, HDR brachytherapy was performed with 7 Gy per fraction for a total of four fractions. For each treatment fraction, a separate insertion of the 60° tandem-ring applicator (GammaMed, Varian Medical Systems, Palo Alto, CA) was performed (figure 1). The tandem lengths were 60mm for four patients, 40mm for three patients, and 50mm for one patient. The same applicator characteristics were used for a given patient for all fractions. Tandem, ring, and needles were used for two patients whereas only tandem and ring were used for the rest. The applicator was introduced into the vaginal cavity, and wet gauze was applied to its front and rear sides to secure it in place. During this insertion process, patients were positioned on a bed board, and a fixation device was utilized to firmly attach the applicator to the bed board, minimizing any movement during patient transfer. Twelve fractions were considered in total.

Data Acquisition and Treatment Planning

Following applicator insertion, patients were scanned on a GE 1.5T Optima 450w MR simulator. Paraxial T2 propeller, para coronal T2 propeller, para sagittal T2 propeller and sagittal 3D T2 CUBE MR sequences were acquired with the specification described in table 1. The sagittal 3D T2 CUBE sequence was used for visualizing and placing the applicator template (3D model of the applicator loaded in the treatment planning system (TPS)) on the para-axial images during brachytherapy planning. The residual Gross Tumor Volume (GTV) (i.e. the Volume of the tumor remaining after external beam radiation)

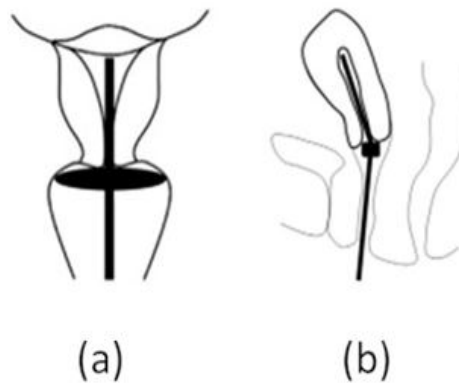


Figure 1: (a) Schematic drawings of correctly inserted uterine tandem with ring applicator. (b) The edge of the uterine tandem needs to be placed in the uterine fundus.

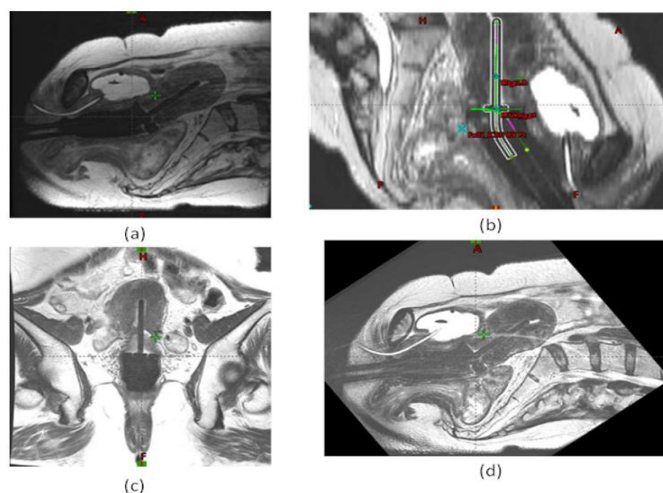


Figure 2: Illustration of the four sequences that were acquired. (a) sagittal T2 CUBE slice, (b) sagittal slice of a paraxial T2 propeller with superposed applicator, (c) para coronal T2 propeller slice and (d) para sagittal T2 propeller slice.

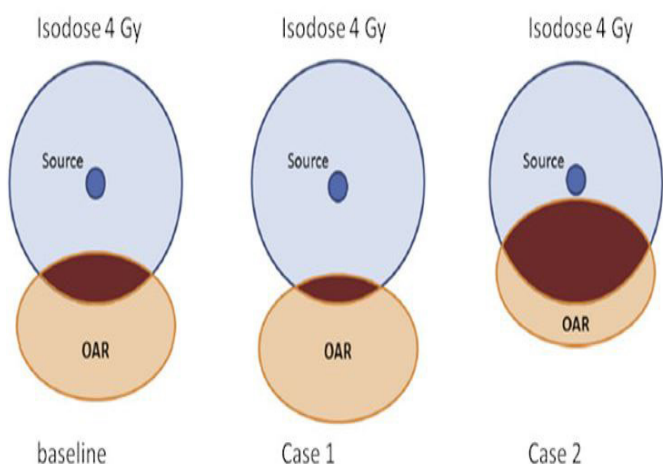


Figure 3: Illustration of the evolution of the intersection between the 4Gy isodose and the OAR between the reference and additional acquisitions. Case 1: the volume of intersection decreased, causing the OAR to move farther away from the implant. Case 2: the volume of intersection increased, causing the organ to move closer to the implant.

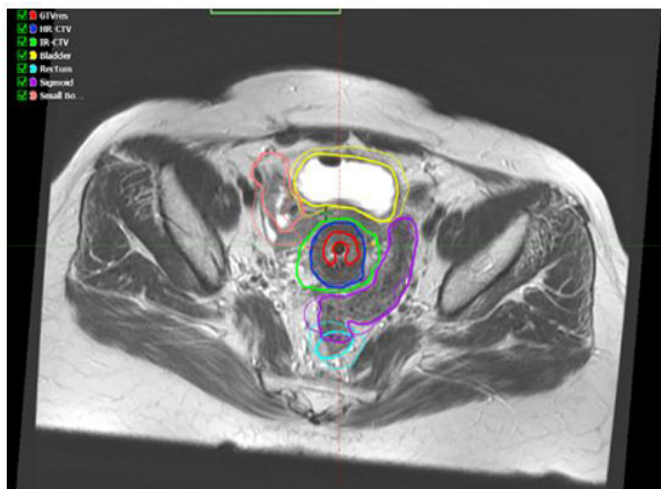


Figure 4: Superposition of OARs (bladder (yellow), rectum (cyan), sigmoid (purple), small bowel (pink)) and CTV (HR-CTV (blue), IR-CTV (green)) contours from MRI₁ to MRI₂ after rigid registration. Thick lines represent OARs delineated on MRI₂ geometry whereas normal lines represent OARs delineated on MRI₁ geometry and transferred to

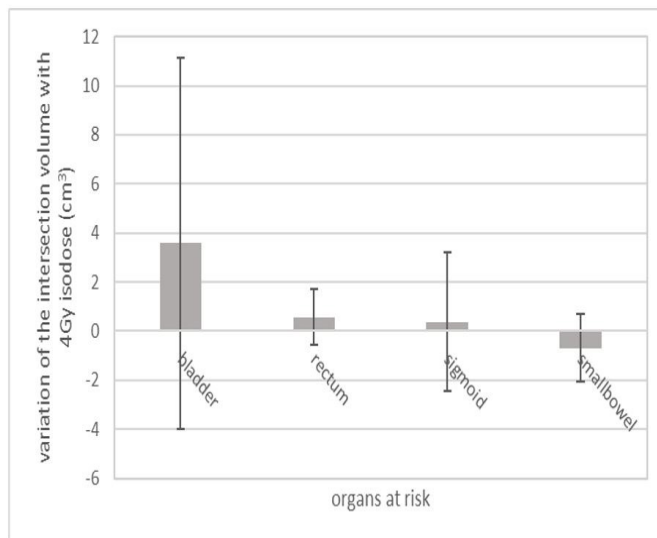


Figure 6: Variation of the volume of intersection between the OARs and the 4Gy isodose between the second MRI (MRI₂) and the planning MRI (MRI₁).

appears as hyper-intense in T2 weighted sequences. Accurate delineation of the residual GTV was done on the paraxial T2 where the imaging plane was parallel to the tandem. Para sagittal and para coronal were used to facilitate the delineation of the OARs on the paraxial scan. Figure 2 shows an example of the acquired sequences.

The residual GTV, the high-risk clinical target volume (HR-CTV), and the intermediate-risk CTV (IR-CTV) were delineated by the radiation oncologist according to the Groupe Europeen de Curietherapie -European Society for Radiation Oncology recommendations, as well as the rectum, the sigmoid colon, the small bowel and the bladder (7,8). The high-risk clinical target volume (HR CTV) encompasses the entire cervix and regions prone to high-risk recurrence due to the presence of visible residual tumor after external beam radiotherapy (EBRT). Administering the maximum possible dose to this volume is crucial for eliminating all residual macroscopic tumors. On the other hand, the intermediate-risk clinical target (IR CTV) includes regions where there was visible tumor present at the initial diagnosis (pre-EBRT),

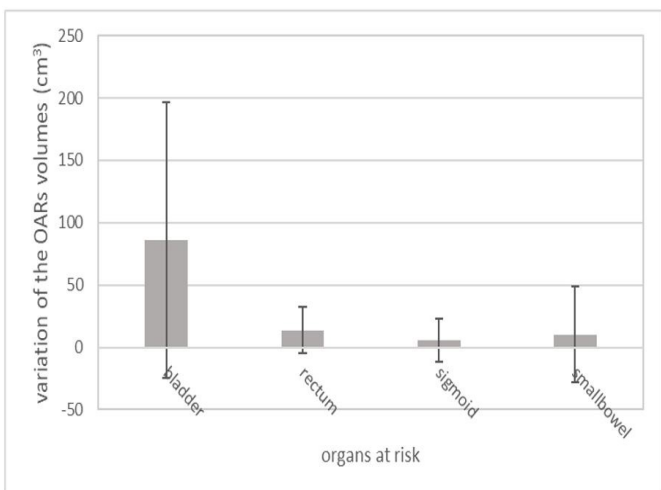
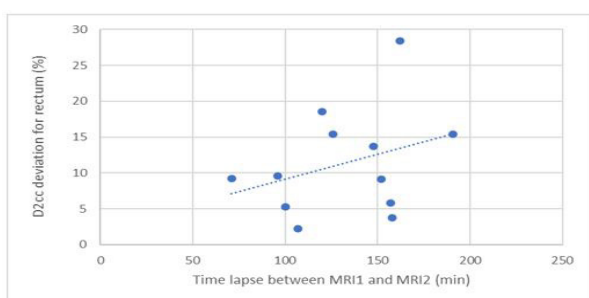
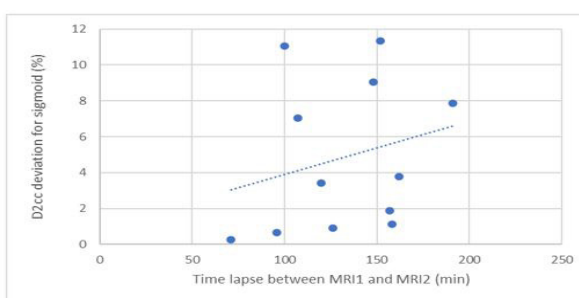


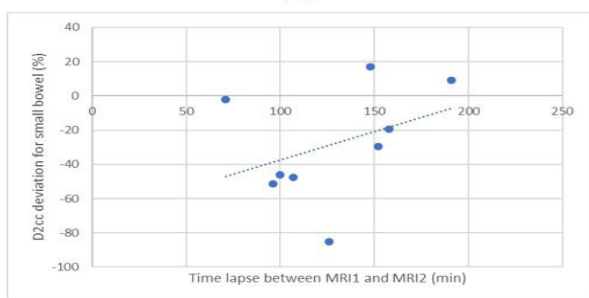
Figure 5: Variation of the volumes of OARs between the second MRI (MRI₂) and the planning MRI (MRI₁).



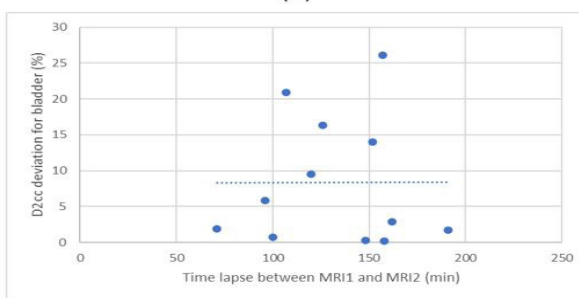
(a)



(b)



(c)



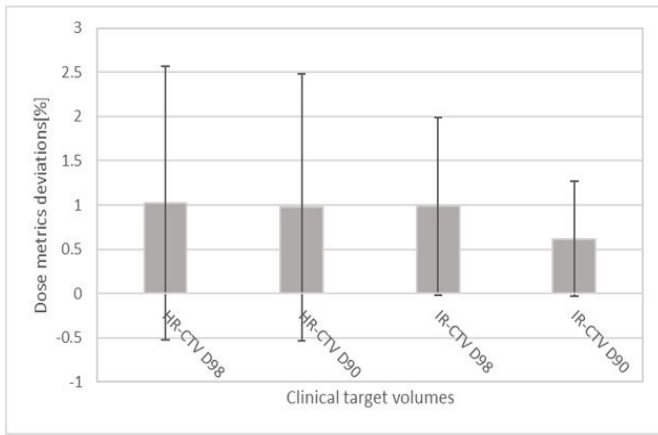
(d)

Figure 7: Scatter and trendline representing the percentage of D2cc deviation ((a) rectum, (b) sigmoid, (c) small bowel, (d) bladder) for time lapses between MRI₁ and MRI₂ of each fraction.

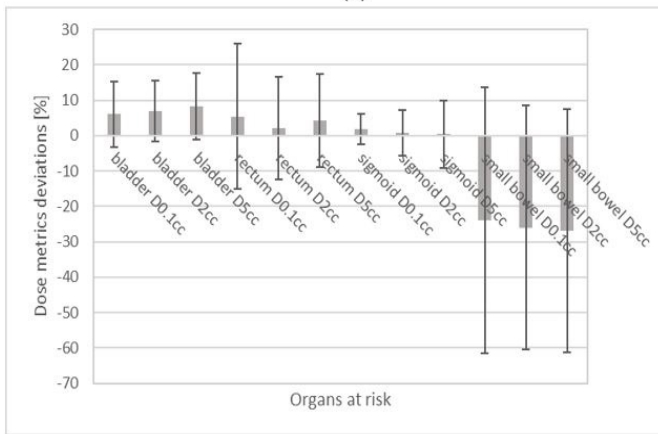
Table 1: Details of the MRI sequences acquired for the MR based planning of cervix cancer treatment in our clinic.

MRI type	Slice size	Voxel size (mm ³)	TR (ms)	TE (ms)	FA (°)
Sagittal 3D cube T2	512×512	0.5×0.5×0.7	2000	57.6	90
Para-axial T2 propeller	512×512	0.7×0.7×3.3	6847.6	97.24	140
Para-coronal T2 propeller	512×512	0.5×0.5×3.3	4830.78	83.52	140
Para-sagittal T2 propeller	512×512	0.5×0.5×4	8814	104.28	140

Note: TR: repetition time, TE: echo time, FA: flip angle



(a)



(b)

Figure 8: (a) Dose metrics deviations obtained for clinical target volumes: HR-CTV and IRCTV (D_{98} , D_{90}). (b) Dose metrics deviations obtained for OARs: bladder, rectum, sigmoid, and small bowel ($D_{0.1cc}$, D_{2cc} , D_{5cc}).

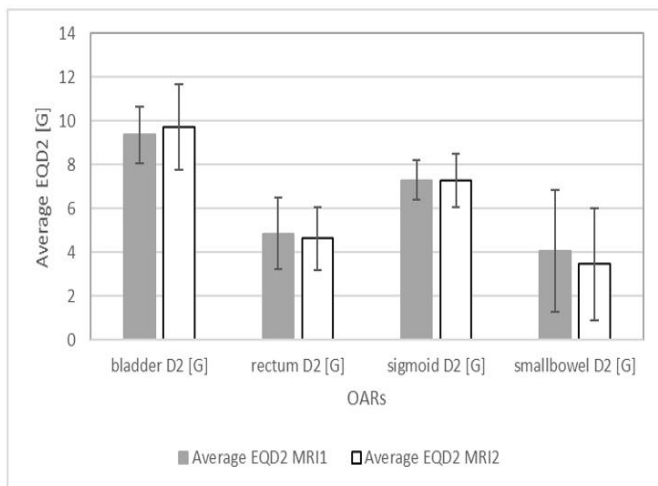


Figure 9: Comparison of average EQD2 for the OARs between MRI1 and MRI2

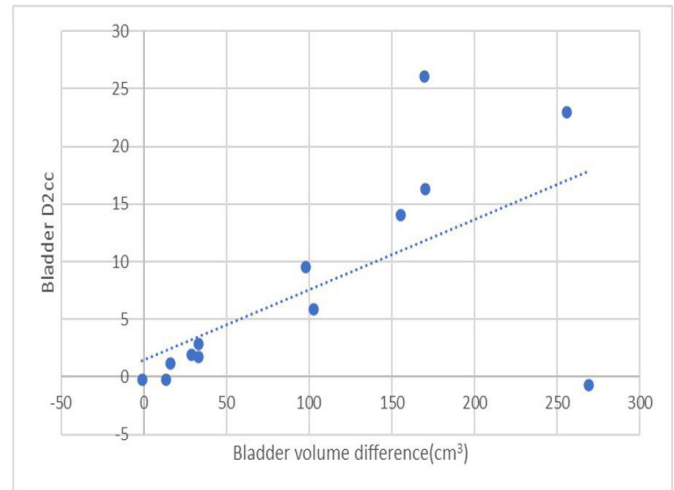


Figure 10: Graph showing the correlation between the difference in bladder volume and the DVH metric D_{2cc} .

but not at the beginning of brachytherapy, thus potentially containing microscopic residual disease.

The treatment plan was optimized on the TPS BrachyVision™ v16.0 (Varian Medical Systems, Palo Alto, CA) to reach the planning aim with dose constraints shown in table 2.

Approximately 30 min prior to brachytherapy treatment delivery, additional MRI sequences were acquired. This consists of paraxial, para coronal and sagittal T2 CUBE with similar parameters to the MRI used for treatment planning. These images are essential for the segmentation of the OARs and clinical target volumes. HR-CTV and IR-CTV were transferred from the reference paraxial T2w MRI (MRI1) to the additional paraxial T2w MRI (MRI2). This requires rigid image registration between MRI1 and MRI2 within the source region. The OARs were contoured by an experienced medical physicist and verified by an experienced radiation oncologist on MRI2.

Geometric comparison

We evaluated the movement of the OARs relative to the sources. A specific isodose level was chosen to create a structure, and this structure remained the same between the reference plan and the additional plan. The points where this isodose intersected with the OARs were tracked on MRI1 and MRI2, providing insights into the movements of the OAR in relation to the implant. Two scenarios are possible. The first is when intersection volume decreases, and the OAR gets farther from the implant than previously (figure 3). The second is when the intersection volume increases, and the organ gets closer to the implant (figure 3). The 4Gy isodose was considered as it is below the dose constraints chosen for the bladder (<5.4Gy) and the sigmoid, rectum, small bowel (<4.5Gy).

Plans Comparison

The dose planned on MRI1 was transferred to the new anatomy defined by MRI2. Dose volume histogram (DVH) metrics were computed for the structures delineated on both MRI2 and MRI1 as recommended by the EMBRACE II protocol(9). The minimum dose to

Table 2: Description of the dose constraints applied for brachytherapy treatment planning of cervix cancer. The minimum dose to 90% and 98% of the structure are D90% and D98% respectively. The minimum dose of the most exposed 2 cm³ volume of the OARs is denoted D2cc.

Structure	Dose constraints
residual GTV	D98% > 8.3 Gy
HR CTV	D90% > 7.8 Gy
IR CTV	D98% > 3.5 Gy
Bladder	D2cc < 5.4 Gy
Rectum	D2cc < 4.5 Gy
Sigmoid	D2cc < 4.5 Gy
Small bowel	D2cc < 4.5 Gy

90% and 98% of the HR-CTV or IR-CTV denoted respectively D90 and D98 were computed. The minimum dose of the most exposed 0.1 cm³, 2 cm³, and 5 cm³ volume of the OARs denoted respectively D0.1cc, D2cc, and D5cc were computed. The percentage of DVH metrics deviations (PDMD) from the reference DVH measurements on MRI1 were computed. Statistical significance of dose differences was assessed using the paired one-tailed Wilcoxon signed-rank test, with a 5% significance level. The brachytherapy dose was converted into the equivalent doses in 2 Gy fractions (EQD2) using the linear model with $\alpha/\beta = 3$ Gy for OARs(10). The average EQD2 per fraction was computed for the OARs and compared between MRI1 and MRI2. Furthermore, the total EQD2 per structure was computed for the whole treatment (external radiotherapy + brachytherapy) where missing fractions (no MRI2 acquisition) were replaced with the dose measurements for the MRI1 based plan.

The effect of the tandem length and the type of the implant on the percentage of D2cc deviation for the bladder was investigated to search possible correlations between the two.

Results

OAR Movement and Volumes change

A volume change and deformation of the OARs between MRI1 and MRI2 was observed for all patients. Figure 4 shows an example of the superposition of the OARs contours after registering rigidly MRI1 to MRI2.

Figure 5 shows the average change in the volume for the bladder, the sigmoid, the rectum, and the small bowel between MRI1 and MRI2. The change in the volumes and geometry of the OARs resulted in changes in DVH metrics (D0.1cc, D2cc, D5cc).

The average intersection volume between the 4Gy isodose and the OARs increased in MRI2 compared to MRI1 except for the small bowel (-0.69 cm³). For the bladder, the rectum, and the sigmoid the intersection with 4Gy isodose increased by 3.57cm³, 0.56cm³ and 0.37cm³ respectively. Figure 6 shows the variation of the intersection volume for the OARs. The PDMD for the OARs was plot as a function of the time lapse between first and second MRI for each fraction. Figure 7 shows an ascending trendline with time for the D2cc deviation of the rectum, the sigmoid and the small bowel. For the bladder, the trendline is almost horizontal showing no obvious dependance between the time lapse increase and the bladder DVH metrics.

Dosimetric Impact

Figure 8a and 8b show average PDMD and standard deviations, obtained for cervix CTVs and OARs respectively. For CTVs, the PDMD were within 1%. The slight differences in tumor coverage are within the uncertainties due to image registrations. The highest PDMD including standard deviation was D98 = 1.02±1.54% for HR-CTV, D98

= 0.98±1% for IR-CTV, and D0.1cc =5.4±20.49% for the rectum in the group of OARs.

Average variations of dose metric remained within 8% for the bladder, 5% for the rectum, and 2% for the sigmoid whereas the values were in the range [-23%, -26%] for the small bowel. A large individual heterogeneity was observed with standard deviations for OARs in the range [4%, 20%] (the bladder, the rectum, and the sigmoid) and [34%, 37%] (the small bowel) respectively.

Figure 9 represents a comparison of average EQD2 for the OARs between MRI1 and MRI2. The EQD2 doesn't change drastically between both MRI which means that the treatment plans are still valid although treatment delivery happens ~3 hours from the application. Furthermore, the assessment of the total treatment (external beam radiotherapy + brachytherapy) based on EQD2 measurements for all the OARs have shown similar success rates to the reference workflow. The PDMD of the bladder was smaller using a tandem length of 60mm compared PDMD obtained for tandem length of 40-50mm.

Discussion

In our clinic, intra-fractional HDR brachytherapy is planned based on MRI only which is the gold standard(6). This study aimed to evaluate the impact of intra-fractional organs motion in the context of HDR brachytherapy of cervix cancer. This was performed by acquiring additional MR sequences approximately 30min before patient treatment delivery and ~2 to ~3hours after the first MR sequences used for treatment planning. The time interval necessary for the whole workflow is comparable to the range of (3-5h) found in the literature (11) and it includes durations for imaging, contouring, planning, optimizing, reviewing the plan, approving it, and delivering treatment. The same applicator insertion was considered for both MR sequences.

Our results showed that systematic variations of D0.1cc, D2cc and D5cc were minor <5% for the sigmoid, the rectum, and small bowel but with large individual heterogeneity (random variation, standard deviations <20%). These findings align with Nesvacil et al.(4) multi-centric (six centers) study that focused on dosimetric impact of inter- and intra-fractional anatomical variations in fractionated cervix cancer brachytherapy. Three centers analyzed MRI obtained during the insertion of the same applicator (intra-application variation) with an average interval between acquisitions of [5h, 22h] (4).

The bladder presented a statistically significant PDMD of D2cc = 7± 8% which was correlated with the change in the bladder volume (patient with high difference in bladder volume, had high PDMD of the latter). This is shown in figure 10; a linear trendline where the PDMD increases with the augmentation of bladder volume is obtained. Although the bladder was filled with the same amount of saline as for MRI1, volumes differences between MRI1 and MRI2 were observed that can be attributed to patient hydration. This suggests that careful bladder filling strategies will probably reduce PDMD.

The time between the acquisition of the planning MRI and the treatment delivery influences the amount of dose received by the OARs due to intra-fractional motion; Figure 7 showed a linear correlation between the percentage deviation of D2cc and the time interval ($\Delta t = t_{MRI2} - t_{MRI1}$) for the rectum, the sigmoid and the small bowel with PDMD increasing with Δt . For the bladder, the trendline was found horizontal; this could be explained by the same bladder filling done prior to MRI1 and MRI2 acquisitions which may lead to constant dose deviations. The deformation of the rectum due to gas and filling with time could explain the increase of dose deviations compared to MRI1. This shows that intra-fractional motion and consequent dose deviations could be decreased by reducing the duration between MRI1 acquisition and treatment delivery to 1 or 2h. Artificial intelligence offers interesting solutions for this issue as it enables performing automatic

segmentation and treatment planning within few seconds/minutes (12).

The PDMD to the bladder varies according to the tandem length and the complexity of the implant (with or without needles). Longer tandem may allow the radioactive source to be positioned farther away from the bladder. This can lead to a more favorable dose distribution with potentially lower radiation exposure to the bladder. With a short tandem the radioactive source is positioned closer to the cervix. This may result in higher radiation dose to the immediate vicinity of the cervix, potentially increasing the dose to the nearby bladder. The intra-fraction dose to the bladder increases with short tandem, which means that the time lapse between MRI1 acquisition and treatment delivery should be reduced for shorter tandems. The conclusions are similar when needles are used.

Yan et al. (2) also examined the dosimetric impact of intra-fractional organs movement in brachytherapy of cervical cancer. The pre-delivery CBCT was acquired and compared to the planning CT. The main disadvantages of this approach are difficulties in delineating OARs especially on CBCT due to low image quality and applying extra-radiation to the patient. Compared to this study (2), our delineation procedure could be more accurate as it benefits from high soft tissue contrast offered by the MRI (6).

Understanding the impact of OAR movements and their potential unforeseen clinical implications, proactive measures are necessary to address this phenomenon. Nevertheless, the considerable heterogeneity observed among patients poses challenges in straightforwardly reducing dose constraints without adversely affecting some patients. Mazon et al.(3) described some solutions to be investigated. First, adjustments to clinical protocols might be made to reduce the amplitude of these movements. For example, a drainage tube in the rectum which is used for in-vivo dosimetry purposes might facilitate the evacuation of gas and counteract rectal filling during the treatment delivery. Similarly, bladder filling can be prescribed between imaging and treatment delivery. The degree of bladder filling, however, is subject to variation in each case. Maintaining a balance between a 2cc dose to the bladder (which may be elevated for a fully distended bladder) and a 2cc dose to the small bowel (which may be heightened in the case of an empty bladder, as the loops could encroach upon the treatment region) is crucial. The bladder filling for treatment should be recreated as it was there during imaging. Second, live monitoring of the dose can be performed using ultrasound monitoring which can lead to treatment interruption if significant movement of the OARs is observed, or the dose delivered can be adapted in the next fractions. Last, patients presenting high dose variations in the OARs could have the margin applied to the GTV adapted. This procedure necessitates a careful evaluation as it may lead to underestimation of the doses delivered to HR-CTV and IR-CTV.

There are some limitations to this study. This study is conducted on a single institution with a small number of patients. A wide heterogeneity between patient fractions was observed. While dosimetric variations due to organs movement were minor for the sigmoid and rectum, statistically significant variations were observed for the bladder and small bowel. Adaptive inter-fractional HDR brachytherapy was implemented by re-imaging the patient before each fraction and planning on the new images. However, implementing an intra-fractional MRI-based adaptive treatment procedure was not feasible due to the lack of real-time imaging.

Future work will consist of performing a multicentric study with more patients. Also, a patient follow-up will be carried out to assess the impact of the dosimetric variations on the treatment response, morbidity, and on patient quality of life.

Conclusions

We evaluated the impact of organs movements in HDR cervical brachytherapy using second MRI acquisitions. MRI offered better delineation accuracy thanks to high soft tissues contrasts. Minor dosimetric variations (below 5%) for the rectum and the sigmoid were obtained. For the bladder, D2cc was 7%. The small bowel was better spared as it presented negative percentage of dose metrics deviations. These results presented discrepancies between patients. Further data from multiple centers are necessary to enhance our conclusions.

Ultimately, individualized solutions are necessary to minimize OAR exposure while delivering curative doses to the tumor. This personalized approach will ensure optimal patient care and minimize treatment-related complications.

Disclosure

Ethics approval and consent to participate

The local Ethics committee (Hamad Medical Corporation HMC, Doha, Qatar) approved this study (protocol number MRC-01-21-697) and all participating patients provided their signed consent before undergoing imaging procedures.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans <http://www.wma.net/en/30publications/10policies/b3/index.html>; EU Directive 2010/63/EU for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm; and the Uniform Requirements for manuscripts submitted to Biomedical journals <http://www.icmje.org>.

Informed consent was obtained for experimentation with human subjects.

Competing Interests

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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