MRI-based pre-planning in patients with cervical cancer treated with three-dimensional brachytherapy

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Objective: The aim of this study was to analyse the feasibility and determine the benefits of MRI-based pre-planning with CT/MRI data fusion in patients with cervical cancer treated with radical radiotherapy.

Methods: Patients underwent MRI examination prior to external beam radiotherapy and prior to the first and fourth fraction of brachytherapy with applicators in place. Insertion of applicators at the radiology department was performed under paracervical anaesthesia. The benefit of MRI pre-planning was determined by comparing conventional treatment planning with dose specification to “point A” and dose specification to 90% of the high-risk clinical target volume (HR-CTV D90). Tolerance of MRI evaluation with applicators, coverage of HR-CTV and dose–volume parameters for organs at risk (OAR) has been assessed in 42 brachytherapy procedures.

Results: Insertion of applicators at the radiology department was successful in all patients and there were no complications. The target dose was higher for MRI planning than for conventional planning (5.3 Gy vs 4.5 Gy). Maximum doses in the bladder and rectum were significantly lower ($p < 0.05$) for MRI planning than for the conventional approach (6.49 Gy vs 7.45 Gy for bladder; 4.57 Gy vs 5.06 Gy for rectum). We found no correlation between the International Commission on Radiation Units (ICRU) point dose for OAR and the maximum dose in OAR. Nevertheless, a strong correlation between the maximum dose in OAR and the minimal dose in a volume of 2 cm³ has been observed.

Conclusion: MRI-based pre-planning with consecutive CT/MRI data fusion is feasible and safe, with the advantage of increasing the dose to the tumour and decreasing the dose to the organs at risk.

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Brachytherapy plays a major role in the therapeutic management of patients with cervical cancer [1–4]. Classical brachytherapy techniques used ²²⁶Ra introduced with an applicator. The Stockholm and Paris methods for intracavitary radiation were described as early as 1914 and 1919. Modern techniques are based on afterloading devices (¹³⁷Cs, ¹⁹²Ir) where application and irradiation are separated from each other. During the last three decades, the development of remote afterloading machines has enabled complete radiation protection. High dose rate (HDR) brachytherapy using remote afterloading systems has been widely accepted, particularly for the treatment of gynaecological tumours.

Clinical approaches in brachytherapy are based on treatment principles established more than half a century ago. In patients with cervical cancer, treated with intracavitary brachytherapy, the dose is prescribed at a selected reference “point A”. This point is defined as a spot 2 cm lateral to the cervical canal and 2 cm superior to the ovoids. The dose for OAR is reported using individual

points for the bladder and rectum. In clinical practice, dose calculations are often made from radiographs. In the late 1990s, MRI-guided adaptive brachytherapy was first introduced into treatment planning for brachytherapy. MRI allows tailoring of dose distribution according to the tumour topography while sparing critical adjacent organs [5–10]. Target volume definitions for MRI and recommendations for concepts in treatment planning have been published by the Gynaecological GEC-ESTRO Working Group [11–14]. The clinical impact of MRI usage in brachytherapy of cervical cancer was confirmed by Pötter et al [15] in 2007. Image-guided adaptive radiotherapy based on MRI has shown outstanding improvements in outcome: more than 90% local control and less than 5% major morbidity for locally advanced disease. Recently, Dimopoulos et al [16] showed an improvement in local control with image-guided brachytherapy and increasing dose in patients with cervical cancer.

However, MRI is not routinely available in radiotherapy departments, and transport of patients from MRI units to radiotherapy departments is associated with a high risk of bleeding, perforation and significant changes in the position of applicators. As there was no MRI scanner available in our department, MRI evaluation

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with applicators *in situ* was incorporated into clinical practice by using MRI-based pre-planning with consecutive CT/MRI data fusion. This study aimed to evaluate the feasibility of applicator insertion under paracervical anaesthesia directly within the radiology department and to determine the benefit of CT and MRI data fusion for MRI-based treatment planning in comparison with the conventional planning approach.

Methods and materials

Patients and treatment

Patients were treated with either whole-pelvis three-dimensional (3D) conformal radiotherapy or intensity-modulated external beam radiotherapy in a linear accelerator with 18 MV photons with cisplatin 40 mg m⁻² of body surface per week for 5 weeks. The dose prescribed was the International Commission on Radiation Units (ICRU) point: 45 Gy in 25 fractions (1.8 Gy per fraction).

All patients underwent MRI evaluation before the start of the external beam radiotherapy and then again before the first and fourth fractions of brachytherapy with the applicators in place: titanium GammaMed (GammaMed Plus, Varian Medical Systems, Palo Alto, CA) Fletcher-style applicator, diameter of tandem 2.8 mm. Insertion of applicators at the radiology department was performed in all patients under paracervical anaesthesia. Insertion and paracervical block were performed by radiation oncologists. MRIs with the brachytherapy applicators *in situ* were acquired on a 1.5 T scanner (Signa Excite HD, GE Medical Systems, Prague, Czech Republic). T₂ weighted axial, coronal and sagittal fast spin echo sequences (3 mm slice thickness, no gap) were performed for target contouring and fusion with CT images. After the MRI examination, the applicators were removed. Target volumes and OAR were contoured according to the Gynaecological GEC-ESTRO Working Group recommendations [11–14]. Gross tumour volume (GTV) and high risk clinical tumour volume (HR-CTV) were contoured as target structures. The rectum, sigmoid and bladder were considered to be OAR. Treatment pre-plan optimisation and evaluation was based on dose–volume histogram (DVH) parameters for the HR-CTV and OAR [17–26]. The following day, insertion of applicators was performed in congruent topography as on MRI: identical length of the tandem within the uterus; angle between the tandem and ovoids; distance between the tandem and ovoids; distance between the ovoids; angle between the longitudinal axis of the patient and longitudinal axis of the tandem and ovoids. After insertion of the applicators, the patient was transported from the interventional suite to the CT room for a CT scan. Movement of patients is minimised by using a home-made trolley with a CT/MRI-compatible desk; the patients were transported from trolley to CT gantry via the CT table. Insertion of the applicator was carried out on the trolley.

3D reconstruction and registration

For the purposes of CT/MRI registration, we used 9 applicator landmarks: 4 ovoids; top of the tandem; 2 cm, 4 cm, 6 cm and 9 cm from the top of the tandem. In cases

of suboptimal soft-tissue registration (cervix or uterus), soft-tissue landmarks were added and registration was repeated until the results were satisfactory.

3D planning

After the registration procedure was completed, we reconstructed the applicators using CT images. The contours of OAR were modified according to current topography on the CT images. GTV and HR-CTV contours were used from the MRIs. Treatment times for stopping positions were transferred from the pre-plan. Owing to the modification of contours of OAR, adaptation of the treatment plan was necessary. Dose to the HR-CTV was evaluated in terms of covering 90% of the HR-CTV (HR-CTV D90). The prescribed dose was 6 × 5 Gy, corresponding to a total biologically equivalent dose in 2 Gy fractions (EQD2) of 80–85 Gy. Dose–volume constraints for OAR were 70 Gy EQD2 as maximum dose in the most exposed tissues of the rectum (rectum D2cc) and 90 Gy EQD2 in 2 cm³ of the bladder (bladder D2cc) [11, 12, 17, 21]. Patients were irradiated after plan optimisation.

Tolerance and comparison of conventional plans with 3D MRI-based plans

The feasibility and tolerance of MRI examination with applicators *in situ* and the influence of MRI on treatment planning were assessed.

The first analysis evaluated the application procedure at the radiology department. The feasibility of insertion of applicators under paracervical anaesthesia, time of procedure and complications during and after the application were also assessed.

The influence of using MRI for contouring the clinical target volume on treatment planning, and comparison with conventional planning using dose specification to point A, was the second part of the analysis. We created two plans for every application: the conventional approach and the 3D MRI-based plan with dose specification to the HR-CTV D90 limiting the maximum dose in the most exposed tissue of OAR according to the Gynaecological GEC-ESTRO Working Group Recommendations. Evaluation of DVH parameters was performed for HR-CTV of the bladder and rectum. The relationships between point doses (point A, ICRU bladder and rectal points) and DVH parameters (D90, D2cc for rectum and bladder) were evaluated in standard plans and 3D-based plans. Dose comparison was performed using the paired two-tailed *t*-test. Correlation of point doses and DVH parameters was performed using linear regression and correlation analysis. The level of statistical significance was set to *p* < 0.05.

Results

Insertion of the applicators at the radiology department under paracervical anaesthesia was successful in all patients. We observed no complications during the whole MRI procedure at the radiology department (application, MRI scanning and period after removal of applicators). The average time of insertion of applicators

at the MRI room under paracervical anaesthesia was 15 min. Contouring and planning time needed for pre-planning was significantly longer than planning using pre-planning data (77 vs 34 min).

We performed 84 plans for 42 CT/MRI fusions in 7 consecutive patients (14 insertions at the radiology department). The target dose was higher for MRI-based planning than for the conventional planning approach. Mean HR-CTV D90 was 5.3 Gy; mean dose in point A for conventional plans was 4.5 Gy. The difference was statistically significant, $p < 0.05$ (Figures 1 and 2, Table 1).

The maximum dose in the bladder was significantly lower for MRI-based plans than for the two-dimensional (2D) conventional approach. The maximum dose in the bladder (bladder Dmax) for 3D MRI-based and conventional plans was 6.49 Gy and 7.45 Gy, respectively (mean values). Also, the dose in the most exposed tissue of the bladder was significantly lower using the 3D planning approach than the 2D plans. Mean dose in 2 cm³ of bladder (bladder D2cc) for 3D and conventional plans was 4.12 and 4.52 Gy, respectively. Mean dose in ICRU point for bladder (bladder Dicru) was 3.04 and 3.52 Gy, respectively. All results were statistically significant in favour of 3D MRI-based plans (Table 1).

Similarly, the maximum dose in the rectum was significantly lower for MRI-based plans than for standard plans. The maximum dose in the rectum (rectum Dmax) for 3D MRI-based and conventional plans was 4.57 and 5.06 Gy, respectively (mean values). The dose in the most exposed tissue of the rectum was significantly decreased using the 3D planning approach in comparison with 2D plans. The mean dose in 2 cm³ of rectum (rectum D2cc) for the 3D and conventional plans was 2.95 and 3.25 Gy,

respectively, and for ICRU point for the rectum (rectum Dicru) it was 3.41 and 3.79 Gy, respectively. All results were statistically significant in favour of 3D MRI-based plans (Table 1).

We found no correlation between the ICRU point dose for OAR and the maximum dose in organs or the minimal dose in 2 cm³ of tissue. However, we observed a strong correlation between maximum dose in OAR and minimal dose in a 2 cm³ volume (Table 2 and Figure 3).

Discussion

For decades, the conventional dose calculation for intracavitary brachytherapy was based on the information obtained from two orthogonal radiographs with limited visualisation of the OAR, and with no information about the tumour itself. With the introduction of a CT/MRI-based target concept, it is now possible to move from a 2D (using X-ray with prescription to the point A) to a 3D target definition and dose optimisation. Although CT imaging is sufficient for definition of OAR (rectum, bladder, sigmoid), it does not provide information about the tumour topography or the distinction between the uterine cervix and corpus [24, 26–29]. Recently, 3D MRI-guided brachytherapy has been introduced into clinical practice. The first published clinical results demonstrate a reduction in morbidity and improved local control [2, 15, 16]. An MRI scanner was unavailable in our radiotherapy department, therefore, we have developed an alternative technique of MRI evaluation with applicators *in situ* using MRI-based pre-planning with consecutive CT/MRI data fusion. To the best of our

Figure 1. Dose distribution for conventional plan using dose specification to “point A”. Isodose lines: red, 5 Gy (100%); pink, 8 Gy (160%); yellow, 15 Gy (300%). Contours: blue, gross tumour volume; orange, high-risk clinical tumour volume.

Figure 2. Dose distribution for three-dimensional MRI-based plan using dose specification to high risk clinical tumour volume (HR-CTV). Isodose lines: red, 5 Gy (100%); pink, 8 Gy (160%); yellow, 15 Gy (300%). Contours: blue, gross tumour volume; orange, high-risk clinical tumour volume.

knowledge, no data have yet been published on the systematic integration of MRI-based pre-planning with CT/MRI image fusion in patients with cervical cancer. The aim of this study was to evaluate the feasibility of MRI-based pre-planning and the benefits of CT and MRI data fusion for treatment planning.

Insertion of applicators at the radiology department proved to be successful in all patients, with no complications recorded. The duration of MRI contouring and pre-planning was significantly longer than the duration of CT/MRI contouring and planning (77 *vs* 34 min). This approach, using a modification of OAR contours and the adaptation of the treatment plan instead of creating a completely new plan, offers significant time savings. A short planning time is important not only for patients' comfort, but also for minimisation of volume changes in the OAR between CT evaluation and irradiation.

In this study, 3D MRI-based cervical cancer brachytherapy improved the target coverage and reduced the dose to the OAR. The mean dose in point A for conventional plans was significantly lower than the 3D-based approach. The use of 3D MRI-based planning reduced the maximum dose, the mean dose in a 2 cm³ volume, and the mean dose in ICRU the point for the bladder and rectum. The limitations of conventional treatment planning were also confirmed by finding no correlation between the ICRU point dose for OAR and the maximum organ dose.

One of the most significant limitations of MRI-based brachytherapy is the difficulty of visualising the applicators [18, 22, 23]. As the small aperture of our commercially available applicator made the insertion of plastic saline-filled catheters impossible, we focused on the precise delineation of the external contours of our applicator. We achieved the best results with gel-absorbed vaginal

Table 1. Dose comparison of conventional plan with three-dimensional (3D) MRI-based plan registration

	Conventional plan (mean (SD))	MRI-based plan (mean (SD))	Statistical difference (<i>p</i> value)
Bladder			
Dmax (Gy)	7.45 (2.01)	6.48 (1.29)	<0.05
Dicru (Gy)	3.51 (0.59)	3.04 (0.81)	<0.05
D2cc (Gy)	4.52 (0.92)	4.12 (0.74)	<0.05
Rectum			
Dmax (Gy)	5.06 (1.15)	4.57 (0.65)	<0.05
Dicru (Gy)	3.79 (0.39)	3.41 (0.77)	<0.05
D2cc (Gy)	3.25 (0.46)	2.95 (0.37)	<0.05
Target (Gy)	4.51 (0.38)	5.32 (0.78)	<0.05
Volume of 5 Gy (cm ³)	112.46 (17.36)	99.91 (24.70)	<0.05

Dmax, maximum dose; Dicru, mean dose in International Commission on Radiation Units; D2cc, mean dose in 2cm³; SD, standard deviation.

Table 2. Correlation of point doses and dose–volume histogram parameters

	Conventional plan	MRI-based plan
Bladder		
Dicru vs Dmax	−0.14	0.29
Dicru vs D2cc	−0.03	0.39
Dmax vs D2cc	0.85	0.80
Rectum		
Dicru vs Dmax	0.37	0.19
Dicru vs D2cc	0.58	0.10
Dmax vs D2cc	0.89	0.89

Dmax, maximum dose; Dicru, mean dose in International Commission on Radiation Units; D2cc, mean dose in 2cm³.

packing. On T_2 weighted images, such packing with absorbed lubricating gel is markedly hyperintense compared with the hypointense applicator. We also used home-made ovoids with exact geometric specification. The accuracy of CT/MRI fusion based on the applicators is highly dependent on the congruent geometry of the applicators both at MRI pre-planning and at CT application. Therefore, we strictly adhered to identical topography for the applicators; we have also developed a home-made CT/MR-compatible table and clamping method.

The main advantages of MRI-based pre-planning with CT/MRI data fusion are the relatively exact definition of GTV and HR-CTV; easy determination of applicators on CT with minimal risk of inaccuracy of applicator reconstruction; decreased time needed for the planning process with reduction in volume changes of OAR; time-unlimited pre-planning (without personal stress and decreased comfort for the patient due to a protracted contouring and planning process); and the possibility of combined interstitial and intracavitary brachytherapy in patients with suboptimal response after external chemoradiotherapy. An obvious disadvantage is the additional insertion of applicators at the radiology department under paracervical anaesthesia and the necessity of congruent alignment of applicators on MRI and CT scans. Reproducibility of inserted applicators and topography of clinical target volume need to be validated.

Conclusion

This study provides unpublished evidence of the systematic integration of MRI-based pre-planning with consecutive CT/MRI data fusion into clinical practice. 3D MRI-based brachytherapy enables a dose escalation

Figure 3. Correlation of maximum dose in organ at risk to point doses (Dicru) and dose–volume histogram parameters (D2cc). Dmax, maximum dose; Dicru, mean dose in International Commission on Radiation Units; D2cc, mean dose in 2cm³.

to the tumour with an additional benefit of reducing the dose to the rectum and bladder. Our experience suggests that this technique is feasible as well as safe, and might be particularly suitable for those radiotherapy departments where the MRI scanner is in a remote location.

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