

MRI assisted cervix cancer brachytherapy pre-planning, based on insertion of the applicator in para-cervical anaesthesia: preliminary results of a prospective study

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Abstract

Purpose: To report on preliminary results of a prospective study on MRI-assisted cervix cancer brachytherapy pre-planning.

Material and methods: In six locally advanced cervix cancer patients, five days before the first brachytherapy fraction, tandem & ring applicator was inserted under para-cervical anaesthesia, MRI performed and applicator removed. Procedure-time and patient-tolerability were recorded. High risk CTV and organs at risk were delineated, virtual needles placed and dose planning performed. At brachytherapy, insertion was carried out under subarachnoidal anaesthesia, according to pre-planned geometry. Pre-planned and actual needle positions and DVH parameters were compared.

Results: The procedure was well tolerated and short. All inserted needles were inside high risk CTV and outside organs at risk. Differences in pre-planned and actual DVH parameters and implant geometry were small.

Conclusions: The procedure was well tolerated and feasible. Pre-planned geometry could be reproduced thoroughly at brachytherapy application.

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Key words: cervix cancer, MRI, pre-planning, image-guided brachytherapy.

Introduction

In recent years, sectional imaging has been systematically introduced into gynaecological brachytherapy (BT) treatment planning at a growing number of institutions worldwide, with MRI and CT currently representing the most often employed modalities in this field. MRI, due to its high soft tissue depiction quality and multiplanar imaging capability represents a superior imaging approach when compared to CT [1-7]. Its systematic implementation into the process of gynaecological BT planning, according to the GEC ESTRO recommendations [8, 9], allows for an individual assessment of tumour dimensions, topography and patterns of spread (and regression) at time of diagnosis and BT [10, 11]. Post-insertion MRI at time of BT enables an accurate and reproducible delineation of gross tumour volume (GTV), clinical target volume (CTV) and organs at risk (OAR), reconstruction of the source path within the applicator and assessment of its relations to pathoanatomical structures. Utilizing modern treatment

planning systems and remote afterloading technologies permits an individualized adaptation of dwell-times and positions of the ^{192}Ir stepping source within the implanted volume and systematic analysis of resulting dose volume histogram (DVH) parameters. Thus, a conformal dose distribution in the tissue can be achieved, applying tumoricidal doses in the target volume while respecting OAR dose constraints. In cases of CTV extension beyond the reach of a standard isodose distribution of the intracavitary (IC) application, parts of the target volume are not covered with the prescribed dose, leading to cold spots that predispose to treatment failure. A combined IC and interstitial (IS) approach utilizing modified MRI compatible tandem ring applicator with plastic or titanium needles has been proven feasible, safe, accurate and reproducible for this selected subgroup of patients [12, 13]. Favorable dosimetric outcome of MRI-based cervix cancer BT is being reflected in encouraging reports on local control and morbidity rates [14-18].

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At the Institute of Oncology in Ljubljana, we have been using 3D MRI assisted BT in accordance to the GEC ESTRO recommendations for treatment of locally advanced cervix cancer since August 2006. In our treatment strategy, external beam radiotherapy (EBRT: 45-50.4 Gy in 1.8 Gy daily fractions) \pm concurrent chemotherapy (weekly Cisplatin, 40 mg/m²), is followed by two fractions of 3D MRI based pulsed dose rate BT, using a plastic tandem & ring applicator (©2005-2009 Varian Medical Systems, Inc., Palo Alto, USA).

In cases of insufficient response to EBRT and/or unfavorable topography at time of BT, a combined IC/IS application is performed, utilizing a specially designed, home-made ring template-cap for the guidance of plastic needles into the parametria (Fig. 1). Two weekly fractions of biologically equivalent dose of 20 Gy (linear-quadratic model, $\alpha/\beta = 10$ Gy, repair half-time = 1.5 hours) are prescribed to the high risk CTV (HR CTV). The optimization of the dose distribution is performed according to our departmental dose-constraints and loading pattern rules. We aim to achieve a D90 for the HR CTV exceeding the prescribed dose and a V100 of > 90-95%, while respecting our dose limits for the OAR. We aim to keep the minimal dose to the most exposed 2 cm³ of the rectum, sigmoid colon and bladder (D2cc) below 10, 10 and 12.5 Gy, per BT fraction, respectively (linear-quadratic model, $\alpha/\beta = 3$ Gy, repair half-time = 1.5 hours). Therefore, a summary of the equivalent biological doses from EBRT and two BT fractions leads to a planned D90 for the HR CTV exceeding 90-95 Gy while the total D2cc for the rectum, sigmoid colon and bladder is aimed to be kept below 65-70, 65-70 and 70-75 Gy, respectively. When loading of the IS needles is indicated, the dwell-times for the needle source positions are restricted below 20% of the tandem dwell-times.

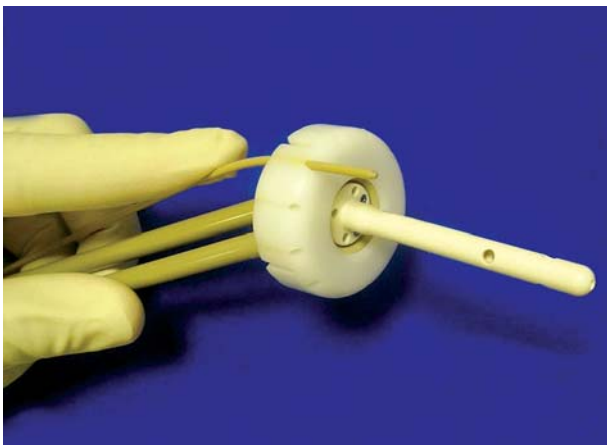


Fig. 1. MRI compatible plastic tandem & ring applicator (©2005-2009 Varian Medical Systems, Inc., Palo Alto, USA) with a specially designed, home-made ring cap attached. The holes are drilled through the cap which serves as a template for guidance of plastic needles into parametria. The holes are equidistant and parallel with the uterine tandem. In the example on the Figure, a plastic needle is inserted in one of the ring holes to a depth of 1.5 cm

Based on encouraging results of our previously published pilot study [19], a prospective protocol is currently under-way at our institution to systematically address various aspects of BT pre-planning in MRI assisted cervix cancer BT. The purpose of our study is to assess possibility of patient tolerance and time needed for MRI-assisted BT pre-planning, based on insertion of IC tandem & ring applicator in regional para-cervical anaesthesia prior to the actual implantation. We aim to achieve: (1) fast and painless insertion of the IC applicator for the purpose of pre-planning without exposing the patients to risks of general or subarachnoidal anaesthesia, (2) fast acquisition of MRI pre-planning, (3) determination of an optimal distribution of virtual IS needles in addition to the IC component to arrive at an optimal dose distribution and (4) an accurate reproduction of the pre-planned geometry and dosimetry at time of actual implantation. We report on the preliminary results in this protocol.

Material and methods

Patients and tumours

The study protocol has been approved by our institutional and national ethics committee. Six consecutive cervix cancer patients with locally advanced biopsy proven squamous-cell carcinoma (four FIGO stage IIb and two IIIb) treated with curative intent at our institution from July 2008 to March 2009 were included in the study. In five patients, the mean initial tumour width, thickness and height, as measured from the MRI at time of diagnosis were 52 (st. dev. 7) mm, 43 (st. dev. 9) mm and 42 (st. dev. 13) mm, respectively. The remaining one patient was referred for treatment from another institution and the initial MRI was not available for analysis. In this case, the initial tumour width, as assessed by clinical examination was 5 cm.

Applicator insertion for pre-planning

Pre-planning procedure was scheduled immediately following EBRT, 5 days before the first BT fraction. Patient preparation consisted of a light meal and a laxative suppository on the evening before insertion and anxiolytic drug (Midazolam 7.5 mg orally) on the morning prior to procedure. After topical application of 10% lidocaine spray on vaginal mucosa, regional anaesthesia was applied by injecting 3 ml of 2% lidocaine bilaterally in the para-cervical region (Fig. 2). Following cervical canal dilatation, a modified tandem/ring applicator in which the ring constitutes a template allowing placement of needles into the parametria (Fig. 1) was inserted and vaginal packing performed.

Pre-planning MRI and applicator removal

Pre-planning MRI was carried out immediately after applicator insertion at a 1.5 Tesla MRI scanner (Siemens Magnetom Avanto, ©2006 Siemens AG, Erlangen, Germany), using a pelvic surface coil. T2 weighted fast spin echo (FSE) images (slice thickness 3 mm, interslice gap

0.9 mm, in-plane pixel size 0.6×0.6 mm, field of view 20×20 cm, matrix size 320×288 , echo time 98 ms, repetition time 5700 ms, flip angle 90°) were obtained in para-transverse (perpendicular to the cervical canal) orientation. Imaging in para-coronal and para-sagittal orientation was omitted to reduce the total imaging time. As an alternative, a T2 weighted 3D fast recovery fast spin echo (FRFSE) sequence (176 slices, isotropic voxel size of 1 mm, field of view 40×40 cm, matrix size 384×386 , echo time 131 ms, repetition time 1500 ms, flip angle 150°) was performed. Image data sets were transferred to the TPS (Brachyvision, version 8.5, Copyright ©1996-2008 Varian Medical Systems Inc., Palo Alto, USA) and co-registered, using shared DICOM coordinates. Manual registration corrections were applied in cases where patient movement occurred between sequences. Immediately after imaging, the applicator was removed and the patient was discharged after 8 hours of observation.

Pre-planning

HR CTV, rectum, sigmoid colon and bladder were delineated according to the GEC ESTRO recommendations [8, 9] and the applicator reconstructed. The pre-planning process commenced by creating a standard IC pre-plan with dose prescription at point A (Fig. 3A). Following evaluation of the resulting isodose distribution and DVH parameters, the IC pre-plan was modified in order to meet our departmental dose constraints for the OAR. Subsequently, virtual IS channels were placed at optimal positions in the para-cervical region, taking into account the degrees of freedom for guidance of parametrical needles, offered by our modified tandem & ring applicator (Figs. 1 and 3B). The needles were positioned and loaded during an iterative manual process, respecting our loading pattern rules and dose constraints. The result of this process was the optimized IC/IS pre-plan. Virtual needle insertion coordinates and depths in the tissue were measured from the pre-planning MRI and recorded. Needle insertion coordinates were defined for a given ring diameter in para-transverse image orientation, one slice above the ring surface by measuring the angle between the antero-posterior patient axis and the line, connecting the center of the tandem and the respective needle (Fig. 3B). V100 and D90 for the HR CTV (expressed as percentage of the prescribed dose) and D2cc for the OAR (expressed as percentage of the dose constraint) of the standard IC pre-plan and optimized IC/IS pre-plan were recorded.

Actual insertion, imaging and treatment planning

At time of the first BT fraction, the insertion was performed under subarachnoidal anaesthesia. In addition to the modified IC tandem & ring applicator, the IS needles were inserted through the ring template, respecting the pre-planned implant geometry (Fig. 3C). T2 weighted FSE MR images in para-transverse, -coronal and -sagittal orientation were obtained and FRFSE sequence was performed (imaging details above). HR CTV and OAR were delineated and the applicators reconstructed. During treatment planning, the strategy as described above was

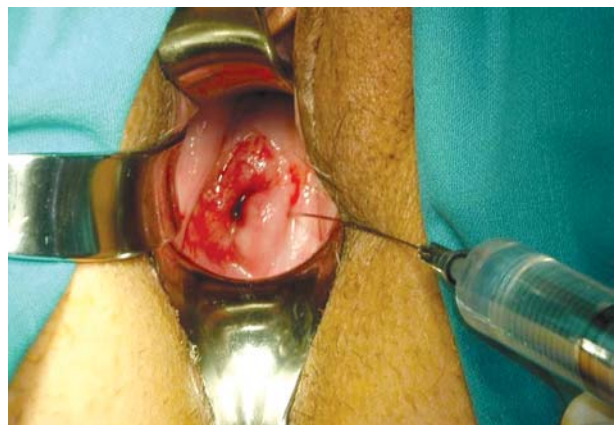


Fig. 2. Injection of anaesthetic into para-cervical regions prior to intracavitary applicator insertion for the purpose of pre-planning. Macroscopic residual tumour after 45 Gy of external beam radiotherapy and concurrent chemotherapy can be distinguished on the right side of the portio

applied: the optimization process commenced by creating a standard IC plan with dose prescription at point A, followed by modification of the standard plan and finally by utilization of dwell positions in the actual IS needles, resulting in optimized IC/IS plan (Fig. 3C).

Actual needle insertion coordinates and depths were measured from the planning MRI (Figure 3C, 3D). V100 and D90 for the HR CTV (expressed as percentage of the prescribed dose) and D2cc for the OAR (expressed as percentage of the dose constraint) of the standard IC plan and optimized IC/IS plan were recorded.

Time and tolerability of the pre-planning insertion

Pre-planning procedure time, including patient preparation in the operating theatre, para-cervical anaesthesia, applicator insertion, MR imaging and applicator removal was recorded.

Pain and tolerability of the IC applicator insertion for pre-planning was assessed subjectively by patients during application, utilizing a 10-tiered visual analogue scale [20]. The insertion was to be interrupted and omitted in case of pain reported by a patient, exceeding level 3.

Reproducibility of pre-planned geometry and dosimetry at actual brachytherapy

Geometric and dosimetric quantifiers of the pre-planned virtual implant were compared to the values, obtained at the first BT fraction. To estimate the geometric reproducibility of pre-planned implant topography, the differences between pre-planned and actual needle insertion coordinates and depths in the tissue were calculated (Fig. 3D). In order to quantitatively assess the ability to reproduce the pre-planned dose distribution at actual planning, the pre-planned V100 and D90 for the HR CTV and D2cc for the OAR were compared to respective values obtained during actual BT. To estimate the dosimetric benefit, acquired by the optimized IC/IS

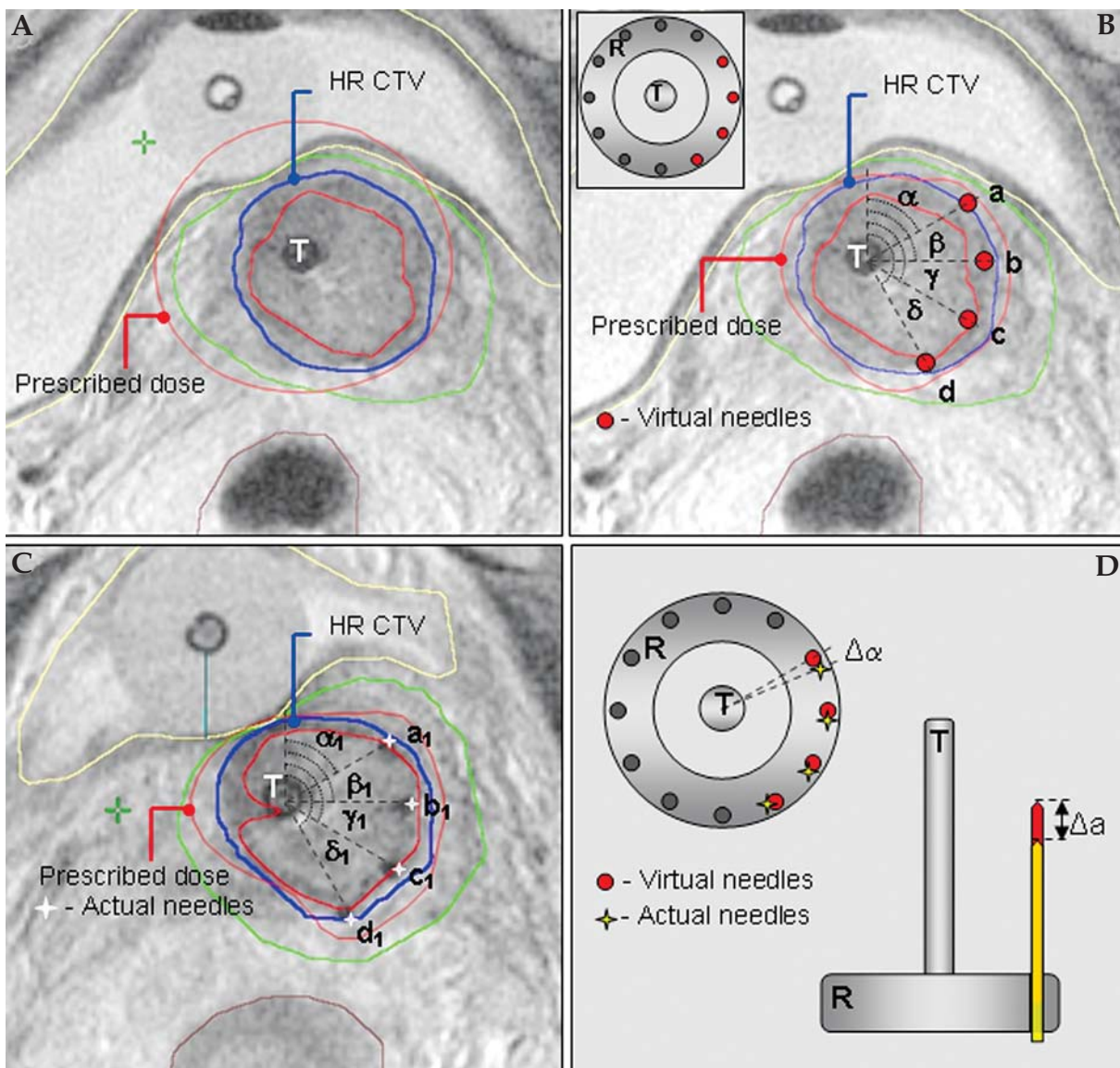


Fig. 3. T2-weighted pelvic MRI in para-transverse (perpendicular to cervical canal) orientation with the applicator in place at time of pre-planning and actual brachytherapy. Schematic representation of the principal steps of the pre-planning process. (A) Pre-planning MRI, acquired after insertion of the intracavitary tandem/ring applicator in para-cervical regional anaesthesia. Isodose distribution of a standard intracavitary treatment plan with dose prescription at point A has been superimposed to the MRI. There is an adequate coverage of the HR CTV with the prescribed isodose. However, the prescribed isodose extends to the bladder, exceeding our departmental dose constraints for this organ. Reducing the tandem dwell-weight in order to spare the posterior bladder wall would compromise the coverage of the left part of the HR CTV due to unfavorable topography between the applicator and the patho-anatomical structures. (B) Virtual optimized intracavitary/interstitial pre-plan. After reducing the tandem dwell weight, four virtual interstitial needles were placed at optimal positions within the target volume, respecting the degrees of freedom, offered by the ring cap template (see insert in the Figure). Treatment plan optimization, utilizing needle dwell positions in addition to the intracavitary component, resulted in a pre-plan with a conformal dose distribution. The prescribed isodose conformably encompasses the HR CTV while the dose constraints for the bladder are respected. Individual needle insertion coordinates are defined on para-transverse MRI for a given ring diameter as the angle between the antero-posterior patient axis and the line, connecting the center of the tandem and the needle. (C) Planning MRI, acquired at time of actual brachytherapy, following insertion of a combined intracavitary/interstitial applicator. The pre-planned geometry has been respected during actual application. In addition to the intracavitary tandem/ring applicator, four interstitial plastic needles were inserted through the ring template, aiming at the accurate reproduction of the pre-planned insertion coordinates and depths. Actual needle insertion coordinates and depths were recorded. Treatment plan optimization, utilizing both the intracavitary and the interstitial component, resulted in a constructive actual dose distribution, comparable to the pre-planned situation. (D) Schematic representation of assessment of the geometric deviations between the pre-planned and actual implant. For each needle, the difference between the pre-planned and actual needle insertion coordinates and depth was calculated. In the example on the Figure, the deviations for anterior-most needle (needle a) are depicted

T - uterine tandem, *R* - vaginal ring, $\alpha, \beta, \gamma, \delta$ - radial angles, defining virtual needle insertion coordinates at pre-planning, $\alpha_1, \beta_1, \gamma_1, \delta_1$ - radial angles defining actual needle insertion coordinates at time of brachytherapy, *a, b, c, d* - virtual needles at pre-planning, a_1, b_1, c_1, d_1 - actual needles at brachytherapy, $\Delta\alpha$ - difference between the pre-planned and actual angle of needle insertion position, Δa - difference between the pre-planned and actual needle insertion depth

application, based on pre-planning, the DVH parameters of the actual standard IC and optimized IC/IS treatment plans at the first BT fraction were compared. In addition, the mean ratios between the actual D90 for the HR CTV and D2cc for the most exposed OAR were calculated for the standard IC, as well as the optimized IC/IS plan and compared.

Results

Pre-planning procedure time and subjective assessment of pain during the IC applicator insertion under para-cervical anaesthesia were 69 (55-90) minutes, and 1 (0-3) on visual analogue scale, respectively. No complications of the para-cervical anaesthesia, pre-planning insertion or actual implantation were observed. All of the 23 IS needles, inserted during the first fraction of BT according to the pre-planned geometry, were inside HR CTV and outside OAR. The mean absolute differences between the pre-planned and actual needle insertion coordinates and depths in the tissue were 7.2 (st. dev. 5.7) degrees and 0.3 (st. dev. 0.3) cm, respectively. Differences between the mean pre-planned and actual D90 and V100 for the HR CTV and D2cc for the OAR are presented in Table 1. The average ratio between D90 for the HR CTV and D2cc for the most exposed OAR at time of BT was 1.3 for the standard IC plan and 1.8 for the optimized IC/IS plan.

Discussion

Even in a setting of the most sophisticated and applicator geometries, imaging, treatment planning and afterloading technology, the optimal technique of applicator insertion remains a precondition for the success of the 3D MRI based BT. Parallelism, equidistance and insertion accuracy with optimal distribution and depth of the IS channels within the target volume enable tight control and fine-tuning of the dose distribution within the implanted tissue. The inadequacies of a suboptimal application cannot be compensated for by treatment plan optimization without compromising the chance of uncomplicated cure. To assure desired position of the BT

catheters within the target volume, different intraoperative and preoperative pre-planning approaches to MRI guidance of insertion have been suggested.

As far as intraoperative pre-planning is concerned, the most common method consists of temporal interruptions of the application in order to acquire MRI for verification and off-line guidance of insertion. Specialized MRI devices with open configuration and modified approaches with closed-bore systems have been developed to allow imaging concurrent with the application and enable real-time intraoperative pre-planning and image guidance for BT of different tumour sites [21-26]. Real-time MRI guided needle insertion for BT of vaginal recurrence in endometrial cancer demonstrated high accuracy of needle placement and limited toxicity in one study [21]. These techniques, however, require an access to the MRI within the operating theatre. Given the technical complexity, spatial limitations, cost and limited availability of MRI, such methods would probably remain limited to selected specialized institutions.

Most common application strategy in MRI assisted cervix cancer BT currently consists of preoperative guidance of insertion. It is based on clinical and MRI findings at diagnosis and clinical findings just before the BT procedure. The implant geometry is decided upon (1) MRI and clinical evaluation of initial tumour extension and pattern of growth, and (2) clinical assessment of the degree and pattern of remission at time of BT, following EBRT \pm chemotherapy [8, 9]. Planning MRI is performed only after the insertion, limiting the ability for corrections in case of suboptimal implantation. In such cases, the inadequacies from the first application should be taken into account during the subsequent insertion (s) to improve the cumulative dosimetric result.

An additional pelvic MRI without the applicator in place, performed after the course of EBRT and before the first BT, permits for more accurate assessment of the extent and topography of residual disease. It adds valuable information to the pre-insertion clinical findings and facilitates the process of performing an optimal implant already at the first application. This approach has been used at our institution in selected clinical situations with challenging tumour topographies in the past. However, a direct

Table 1. Results of the analysis of the pre-planned and actual DVH parameters of the standard intracavitary and optimized intracavitary/interstitial treatment plan

DVH parameter	DVH parameter values for different treatment plans [mean (st. dev.)]			
	Standard Intracavitary		Optimized Intracavitary/Interstitial	
	Pre-planned	Actual	Pre-planned	Actual
D90 (% PD)	115 (36)	119 (30)	112 (7)	113 (7)
V100 (%)	89 (12)	93 (9)	95 (3)	95 (3)
D2cc (% DC)				
Bladder	145 (67)	143 (54)	105 (13)	99 (5)
Rectum	115 (60)	100 (53)	89 (29)	74 (23)
Sigmoid colon	95 (43)	91 (43)	80 (36)	70 (34)

PD – prescribed dose, DC – dose constraint

translation of pre-insertion MRI findings to the condition at time of BT is hindered by the change in spatial interrelations between the patho-anatomical structures, induced by the insertion of the IC applicator at time of BT.

Therefore, in order to enable a comparable pelvic topography at time of pre-planning and BT, the pre-planning MRI needs to be obtained with the IC applicator in place. In this way, the pelvic topography at pre-planning can be reproduced at actual BT. This allows exploitation of the pre-planning MRI for the purpose of defining an optimal geometry of eventual IS implant. This method has been applied with excellent clinical results by others (Lindgaard J, unpublished data), the main limitation of the approach being the need for general or spinal anaesthesia for pre-planning insertion with its inherent risks.

The technique, described here, mitigates this limitation. In our method, the dilatation of the cervical canal and applicator insertion for pre-planning is achieved in para-cervical regional anaesthesia. Using this method, an excellent procedure tolerability could be achieved. In the present analysis, the mean level of pain, as assessed subjectively by the patients, utilizing a 10-tiered visual analogue scale [20], was 1. No patient reported pain exceeded level 3 and in all cases the procedure could be carried out without interruptions. There were no acute complications of para-cervical anaesthesia or the insertion.

A potential drawback of our pre-planning approach is the need for an additional MRI study, increasing the operating time of the MRI scanner which may represent a demand that is difficult to meet in a busy clinic. However, the valuable information, acquired by this additional imaging, permits for a virtual optimization of the implant topography and the dose distribution in the implanted volume. Our results indicate that we have been able to achieve an encouraging reproducibility of the pre-planned geometry of the virtual IC/IS implant at time of actual application. This was demonstrated by small deviations between the pre-planned and actual needle depths and insertion coordinates which was reflected in comparable values of the reported DVH parameters for the HR CTV and the OAR (Table 1). Nevertheless, these encouraging geometric and dosimetric results needs to be verified by including a larger number of patients with different tumour growth patterns. For the current report, no meaningful statistical analysis could be performed due to insufficient number of cases.

In our experience, by respecting the pre-planned geometry, the time needed for the actual application was reduced and the operator confidence and patient compliance during the procedure was improved. In addition, the need for iterative imaging and implant corrections or even removing the applicator due to a potentially suboptimal geometry could be avoided in all cases, which is an important achievement in clinical setting without access to an open MRI inside the operating theater. Importantly, the pre-planning MRI study was performed following a special protocol, including only the acquisition of T2 weighted para-transverse FSE and FRFSE image data sets. Results of our previous study have shown that by utilizing the FRFSE sequence with 1 mm isotropic voxel

size, performing FSE images in para-coronal and para-sagittal orientation can be omitted without compromising the treatment planning process [27]. In this way, the total pre-planning MRI time could be reduced. In our opinion, these listed benefits outweigh the above-mentioned drawback of performing an additional MRI study. In fact, due to its ability to allow an accurate reproduction of the optimal pre-planned geometry already at the first application, the described procedure could potentially serve as a basis for accomplishment of BT in a reduced number of optimized insertions, reducing the total MRI-time and costs.

The mean DVH parameter values for the HR CTV and OAR of the optimized IC/IS actual treatment plan met our departmental dose constraints. Using the combined IC/IS application technique, assisted by our pre-planning approach, the mean ratio between D90 for the HR CTV and the D2cc for the most exposed OAR could increase from 1.3 for the standard IC plan to 1.8 for the optimized IC/IS plan. It can be expected that this improvement in the therapeutic ratio will be translated into favorable clinical outcome in the future.

Conclusions

MRI-assisted pre-planning of BT in locally advanced cervix cancer, based on insertion of the IC applicator in regional para-cervical anaesthesia is an innovative, short, well tolerated and feasible procedure. The pre-planned implant geometry can be reproduced thoroughly at actual BT application, resulting in a favorable distribution of the source channels and, in turn, the dose in the implanted tissue. Further scientific research, based on larger number of patients is needed to assess in detail the geometric, dosimetric and finally the clinical impact of the proposed pre-planning approach.

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