Original paper

Impact of intraoperative MRI/TRUS fusion on dosimetric parameters in cT3a prostate cancer patients treated with high-dose-rate real-time brachytherapy

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Abstract

Purpose: The purpose of this study was to evaluate the impact of intraoperative MRI/TRUS fusion procedure in cT3a prostate cancer patients treated with high-dose-rate (HDR) real-time brachytherapy.

Material and methods: Prostate gland, dominant intraprostatic lesions (DILs), and extracapsular extension (ECE) were delineated in the pre-brachytherapy magnetic resonance images (MRI) of 9 consecutive patients. The pre-implant P-CTV_{US} (prostate clinical target volume) was defined as the prostate seen in the transrectal ultrasound (TRUS) images. The CTV_{MR} includedthe prostate with the ECE image (ECE-CTV) as defined on the MRI. Two virtual treatment plans were performed based on the MRI/TRUS fusion images, the first one prescribing 100% of the dose to the P-PTV_{US}, and the second prescribing to the PTV_{MR}. The implant parameters and dose-volume histogram (DVH) related parameters of the prostate, OARs, and ECE were compared between both plans.

Results: Mean radial distance of ECE was 3.6 mm (SD: 1.1). No significant differences were found between prostate V_{100}, V_{150}, V_{200}, and OARs DVH-related parameters between the plans. Mean values of ECE V_{100}, V_{150}, and V_{200} were 85.9% (SD: 15.1), 18.2% (SD: 17.3), and 5.85% (SD: 7) when the doses were prescribed to the PTV_{US}, whereas ECE V_{100}, V_{150}, and V_{200} were 99.3% (SD: 1.2), 45.8% (SD: 22.4), and 19.6% (SD: 12.6) when doses were prescribed to PTV_{MR} ($p = 0.028$, $p = 0.002$ and $p = 0.004$, respectively).

Conclusions: TRUS/MRI fusion provides important information for prostate brachytherapy, allowing for better coverage and higher doses to extracapsular disease in patients with clinical stage T3a.

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Key words: extracapsular extension, high-dose-rate brachytherapy, MRI/TRUS fusion, prostate cancer.

Purpose

The combination of brachytherapy and external beam radiotherapy (EBRT) is a standard therapeutic option for high risk prostate cancer and has provided excellent results in such patients [1,2]. Brachytherapy allows a high dose of radiation to be administered directly into the prostate with a rapid fall off of a dose to the surrounding healthy tissues [3]. The rapid fall-off over a distance of a few millimetres spares the surrounding structures, but unfortunately may result in uncertain coverage of the immediate peri-prostatic tissue, which may harbour extracapsular extension (ECE), especially in high risk disease where the higher PSA (> 10 ng/ml) and Gleason score (≥ 7) are associated with a likelihood of ECE of approximately 50% [4]. Traditionally, external beam radiation alone has been the basis of treatment for high risk disease, because of assumed better extraprostatic coverage [5]. Among the several radiation techniques available for prostate cancer, brachytherapy offers several advantages in terms of dose conformation, accurately adjusting the isodoses to the prostate while keeping adjacent organs such as the urethra and rectum within tolerance [6]. This precision of brachytherapy requires accurate local staging of disease in

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order to shape isodoses appropriately to cover the target. Common imaging modalities such as transrectal ultrasound (TRUS), have not demonstrated satisfactory sensitivity for detecting, localizing, and staging prostate cancer [3]. Magnetic resonance imaging (MRI) provides high soft tissue resolution to better assess the local extent of disease [7], and the accuracy of MRI in the determination of ECE has been variable across studies. Although it is recognized that the specificity for ECE detection with MRI is high, the sensitivity is rather low [8-10]. Recent studies have shown an increase in sensitivity and specificity for the detection of ECE when using multiparametric MRI as a diagnostic tool in staging [11-13]. The combination of MRI and TRUS is useful for both stereotactic prostate biopsy [14] and staging [15]. Moreover, brachytherapy companies have recently developed software allowing for MRI-TRUS image fusion. Reports have investigated the use of MRI-TRUS fusion for prostate low-dose-rate (LDR) brachytherapy planning [16-18].

The purpose of this study was to evaluate the impact of intraoperative MRI/TRUS fusion on dosimetric parameters in cT3a prostate cancer patients treated with high-dose-rate (HDR) real-time brachytherapy.

Material and methods

Patient cohort

At Cruces University Hospital, HDR brachytherapy is used for the treatment of intermediate and high risk prostate cancer as a conformal boost in conjunction with EBRT. Treatment consists of a single HDR fraction of 15 Gy, followed by 2-4 weeks of EBRT at a dose of 37.5 Gy in 15 fractions over 3 weeks. Nine patients with histologically proven adenocarcinoma of the prostate and clinical (MR imaging) stage T3a disease and without clinical radiographic evidence of metastases were included in this study. All patients were investigated with a serum PSA, TRUS-guided prostate biopsy, and systemic staging with bone scintigraphy and abdominal/pelvic CT. The patient characteristics are given in Table 1.

Table 1. Summary statistics of clinical characteristics

	N
Age (years)	
Mean	68
Range	60-78
PSA (ng/ml)	
Mean	17.7
Range	8.6-29.3
Gleason score	
7	6
8	1
9	1
10	1
% Positive Cores	
< 50%	3
≥ 50%	6
Clinical T-stage	
T1c	7
T2a	1
T2b	1
Pre MRI NCCN risk group	
Intermediate	6
High	2
Very high	1

Magnetic resonance technique

All patients referred to our department for prostate brachytherapy undergo a staging MRI. Magnetic resonance imaging is performed using a 1.5 T Achieva scanner (Philips Electronics, Eindhoven, The Netherlands), and a body multichannel antenna (Cardiac Sense-MS). The parameters of the sequences have been previously optimized for this coil. All patients were studied supine after cleansing rectal enema and intramuscular administration of butyl scopolamine. Axial T1 sequences of the entire pelvis from the iliac crest to pubic symphysis and T2 axial volumetric sequence (VISTA) as a guide for planning brachytherapy were performed. For the functional study, spectroscopy (PRESS) and diffusion (DWI) sequences were performed. The ADC values were obtained from DWI sequences and finally a dynamic FFE T1 volumetric sequence was performed. From the resulting image data, various curves of perfusion were analyzed to detect and localize the tumour. All MR studies were evaluated by radiologists experienced in uro-radiology.

MRI-TRUS fusion

The T2 axial volumetric sequence (VISTA) is imported directly from the picture archiving and communication systems (PACS), and sent to the Oncentra® Prostate v.4.0 software (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). Magnetic resonance images are reconstructed and segmented. Target volumes such as prostate gland, dominant intraprostatic lesions (DILs), ECE, organs at risk (OARs), urethra, and rectum are delineated. A transrectal sagittal volumetric ultrasound image is immediately acquired with images obtained every 2 degrees. A rapid reconstruction algorithm converts the series of 2D images into a 3D volume, which is then displayed in axial, sagittal, and coronal views and transferred to the fusion module. The MR images and the real-time ultrasound examination are displayed on a split-screen with the possibility of overlaying the images live in one image. A graphical user interface is used for rigid manual registration of the ultrasound and MR images. This interface allows for displacements in three dimensions as well as rotations, until both images are correctly superimposed. The contoured structures are transferred to the US dataset. These contours may be slightly modified, until a perfect match with the US images is achieved.

Definition of ECE and target volumes

The parameters studied in MR were established by consensus at our uro-oncology tumour board, and were

defined as: tumour burden (number of nodules or intraprostatic mass), laterality of lesions, the presence or absence of extraprostatic tumor extension, seminal vesicle invasion, pelvic lymph node involvement, and/or metastatic bone disease. The likelihood of ECE was scored based on the presence of indirect or direct signs of ECE. Indirect signs of ECE were defined as tumour contact with the capsule and a capsular signal defect with or without capsular bulging. Direct signs of ECE were defined as the presence of a hypo-intense signal in any periprostatic area (neurovascular bundles, subapical or perivesicular area, recto-prostatic angle and lateral or posterior periprostatic fat). All nine patients included in the study had direct signs of ECE. When seen, extracapsular extension was quantified by measuring the largest radial diameter of extraprostatic tumor, defined as the perpendicular distance of tumor beyond the expected location of the outer capsular margin [19,20], on the transverse T2-weighted images. The prostate gland, dominant intraprostatic lesions (DILs), and ECEs an independent volume were delineated on the pre-brachytherapy MR image sets of the 9 patients by two experienced uro-radiologists. The pre-implant P-CTV_{US} (prostate clinical target volume) was defined as the prostate seen in the TRUS images. To create the planning target volume (P-PTV_{US}), a 3-dimensional expansion of the CTV of 3 mm was performed isotropically, except posteriorly where 1 mm was added. The CTV_{MR} included the prostate with the ECE image (ECE-CTV) as defined on the MR images and an expansion was performed to create the PTV_{MR}.

Treatment and dosimetry

Two virtual treatment plans were performed based on the MRI/TRUS fusion images, the first one prescribing 100% of the dose to the P-PTV_{US}, and the second prescribing to the PTV_{MR}. No changes were made in terms of number and distribution of the needles between plans; however, dosimetric parameters used for inverse planning optimization were modified.

The homogeneity parameters used for optimization aim for prostate V_{100} > 98%, V_{150} of 25-33%, V_{200} < 8%, where V_n is the fractional volume of the organ that receives n% of the prescribed dose, urethral D_{max} (maximum point dose inside the urethral volume) < 115%, and rectal 1 cc < 70% of prescribed dose.

The implant parameters and dose-volume histogram (DVH) related parameters of the prostate, OARs and ECE-CTV were compared between both plans (Table 2).

Statistical analysis

A statistical analysis was performed using the Statistical Package for the Social Sciences, version 20.0 (SPSS, IBM, New York, USA). Descriptive statistics were calculated (means and standard deviations) to summarize the clinical characteristics of the 9 patients and dosimetric indices for each of the two plans. Complete data were available for all parameters considered. Comparisons of the mean values between the two plans for paired data were performed using the *t*-statistic. Significance was defined as a probability value less than 0.05, and no adjustment was made for multiple comparisons.

Results

The mean pre-treatment prostate specific antigen (PSA) level was 17.7 ng/mL (SD: 7.02), mean age 68 years (SD: 6), and mean prostate volume 24.7 cc (SD: 4.4). Sixty-seven percent of patients had Gleason score 7 and 33% had Gleason 8-10. Mean percentage of positive cores in the biopsy was 50% (SD: 28). ECE was located in the prostate base in 5 patients, in the apex in two patients, in the midgland in two patients, and in 8 out of 9 patients involved the posterior-lateral region of the prostate. There was an association between the location of ECE and areas

Table 2. Comparisons of the mean values between the two plans for paired data

Dosimetric parameters	US-Plan		MR-Plan		*p*
	Mean	SD	Mean	SD	
Prostate V_{100}	98.51	0.38	98.43	0.45	0.275
Prostate V_{150}	24.40	3.71	25.80	3.29	0.173
Prostate V_{200}	6.50	1.37	7.07	0.98	0.110
ECE V_{100}	85.94	15.13	99.31	1.20	0.028
ECE V_{150}	18.20	17.27	45.79	22.39	0.002
ECE V_{200}	5.86	6.99	19.57	12.58	0.004
Urethra D_{max}	114.32	1.11	114.33	1.09	0.996
Urethra D_{10}	110.28	1.11	110.01	0.63	0.383
Urethra 1 cc	57.46	45.49	58.23	46.04	0.499
Rectum D_{max}	90.18	13.85	87.10	6.12	0.303
Rectum 1 cc	66.61	3.55	66.59	2.32	0.981
Rectum 2 cc	59.13	3.73	59.33	2.79	0.819

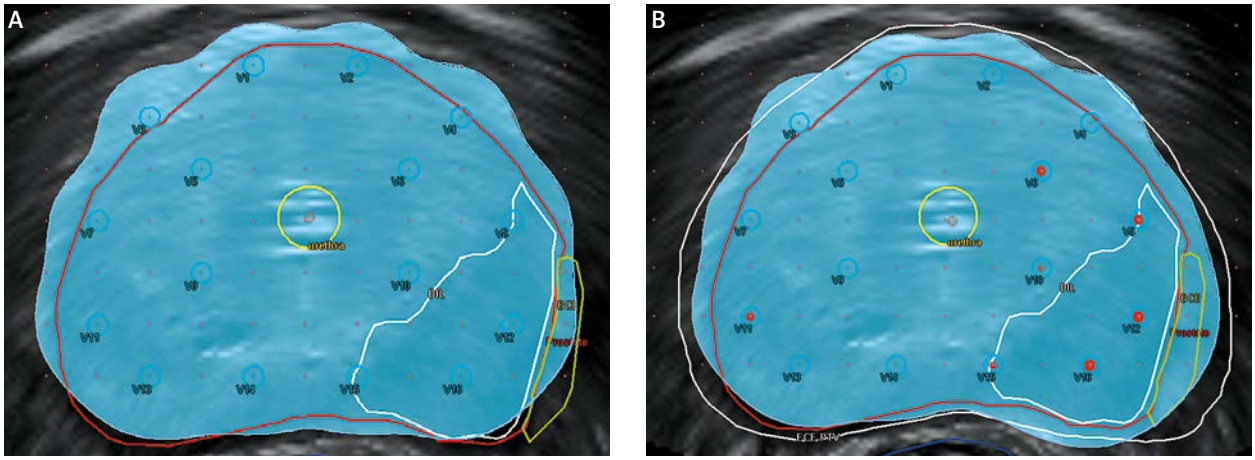

Fig. 1. A) V_{100} isodose (blue color-wash) for the US-Plan. The extracapsular extension (ECE) region (in green) is not covered completely by the prescription dose. B) V_{100} isodose (blue color-wash) for the MR-Plan. The extracapsular extension region (in green) is adequately covered by the prescription dose

of heavy infiltration on biopsy. Mean radial distance of ECE was 3.6 mm (SD: 1.1). The mean number of needles for both plans was 15 (range: 13-17).

Treatment and dosimetric parameters are summarized in Table 2. Mean prostate V_{100}, V_{150} and V_{200} were 98.5%, 24.4%, and 6.5%, respectively for the US-Plan, and 98.4%, 25.8% and 7% for the MR-Plan. Mean urethral maximal dose was 114.3% and was the same for the two plans. No significant differences were found between prostate V_{100}, V_{150}, V_{200}, and OARs DVH-related parameters between the plans. Finally, mean values of ECE V_{100}, V_{150}, and V_{200} were 85.9% (SD: 15.1), 18.2% (SD: 17.3), and 5.85% (SD: 7) when the doses were prescribed to the PTV_{US}, whereas ECE V_{100}, V_{150}, and V_{200} were 99.3% (SD: 1.2), 45.8% (SD: 22.4), and 19.6% (SD: 12.6) when doses were prescribed to PTV_{MR} (Figs. 1 and 2). These differences were statistically significant ($p = 0.028$, $p = 0.002$, and $p = 0.004$, respectively).

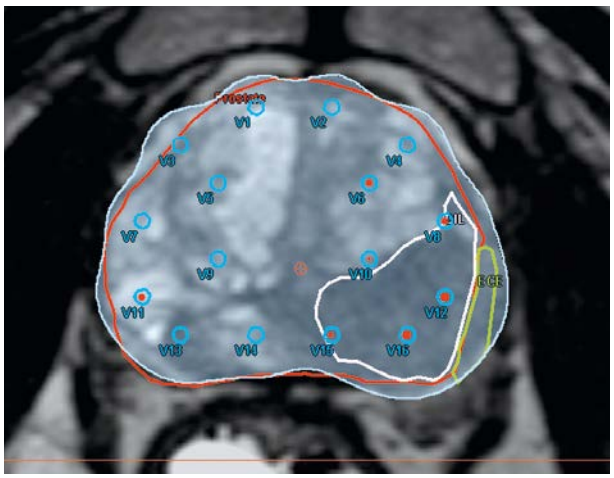

Fig. 2. Fused MR data set. Volumes delineated: prostate (red), dominant intraprostatic lesion (pink), extracapsular extension (green). V_{100} isodose distribution (blue color wash)

Discussion

Our "proof of concept" study shows that TRUS/MRI fusion could provide an important information for prostate brachytherapy, allowing for better coverage and higher doses to extracapsular disease in patients with clinical stage T3a. Technologic and imaging advances have allowed radiation oncologists to reduce the potential risks for treatment-related toxicity, and to escalate dose to the target volume. However, in prostate cancer, neither CT nor TRUS can precisely identify tumour nodules. Therefore, current methods for defining the CTV in prostate cancer may not accurately account for ECE and could lead to underdosage or geographic miss. Effective treatment planning requires accurate determination of the stage of the disease. Various methods have been suggested for predicting that a clinically localized prostate cancer is, in fact, pathologically confined to the prostate [21-24]. Nomograms are limited as a treatment-planning tool, because they do not incorporate anatomic data that could assist in the localization of ECE, which is critical for optimal treatment [4,24,25].

The role of magnetic resonance (MR) imaging in prostate cancer management is expanding as improved MR techniques, such as multiparametric MR and spectroscopic imaging become commonplace, and as experience grows with interpretation of such MR images [26-29]. We recently reported that staging MR impacts staging of the primary tumour, and can modify risk group classification as well as treatment decisions in intermediate and high risk patients. 46% of patients with cT1-T2 were upstaged to cT3 stage when multiparametric MR was performed [30]. In the present study, the clinical stage of the patients before MR was T1c in 7, and T2 in 2 patients. It is important to note that the concept of extra prostatic extension is not a simple binary observation, but has an important quantitative component. The degree of extraprostatic extension affects its detection by MR [31]. McKenna *et al.* [32] observed worse outcomes in patients with greater than 5 mm of ECE on MR. Given the detection of prostate

cancer at an earlier stage through routine PSA screening, ECE at the time of diagnosis is now generally less extensive than in past decades and may not carry the same prognostic significance. Hence, when assessing the accuracy of MR in the detection of ECE it is valuable to stratify by its extent.

Chao *et al*. in a pathologic review of prostatectomy specimens correlated clinical features with the linear extent of ECE to determine the appropriate margin to include in the clinical target volume (CTV) when there is a significant risk of ECE. They demonstrated that the majority of all ECE occur primarily along the postero-lateral region and that approximately 20% of patients who have PSA > 10 ng/ml and biopsy Gleason score > 7 are at risk for ECE extending 4 to 5 mm beyond the prostate capsule [33]. In the present study, only 2 out of 9 patients were found to have ECE greater than 5 mm. The mean ECE radial distance was 3.6 mm, and most of the ECE was located along the neurovascular bundle.

Additionally, previous studies that have investigated the value of MR prior to radiotherapy have consistently shown that MR findings predict biochemical control [32,34-36]. Riaz *et al*. investigated the role of pre-treatment MRI in patients receiving the combination of EBRT and brachytherapy, and showed that the only factors correlating with biochemical control were Gleason score and the presence of extraprostatic extension [37].

The combination of brachytherapy and EBRT is a standard therapeutic option for high risk prostate cancer. The choice between LDR and HDR boost depends on the preference and expertise of the treating physicians, and varies from institution to institution. LDR brachytherapy is used more widely than HDR brachytherapy, although advocates of the HDR technique have noted several potential advantages of this approach [3,38]. The precise control over dose delivery inherent in HDR brachytherapy is not readily achievable with LDR brachytherapy due to factors such as seed or strand migration, post implant prostatic swelling, and the uncertain periprostatic margin, all of which can contribute to suboptimal dose distributions. As far as the coverage of ECE is concerned, manipulation of the dwell times and dwell positions in HDR brachytherapy can correct for deviations in needle placement, tightly control doses to critical organs, and push extraprostatic dose where needed [39]. Several reports have demonstrated improved biochemical control, and higher survival rates with dose escalation using HDR brachytherapy [40-43]. Martinez *et al*. reported a strong dose-response relationship for intermediate and high-risk prostate cancer patients treated with EBRT and an HDR boost [44]. Those receiving a biologically equivalent dose ($BED_{1.5}$) > 268 Gy had significantly decreased biochemical and clinical failures as well as distant metastasis [44]. The $BED_{1.5}$ in our protocol is 318 Gy. The dose administered with brachytherapy (202.5 Gy) represents 64% of the total dose. Hence, an optimal dose distribution with brachytherapy is critical for higher tumour control and better oncologic outcomes.

We have found statistically significant differences in the DVH parameters favouring the MRI-TRUS fusion approach. The V_{100}, V_{150}, and V_{200} of the ECE volume were higher when the ECE was delineated on MR and transferred to the US dataset for planning purposes, while preserving V_{100}, V_{150}, V_{200}, and OAR doses within the pre-established dosimetric constraints.

To our knowledge this is the first study reporting the impact of TRUS/MRI fusion in the coverage of ECE in T3a patients treated with HDR real-time brachytherapy.

We acknowledge several uncertainties in the delineation of DIL and ECE volumes transferred from the MR images to the US dataset due to several reasons: a Foley catheter was not in-situ during the MR acquisition, the transrectal probe may deform the posterior prostate, and two patients received 1 month of hormonal therapy prior to HDR brachytherapy. For these 2, the volume of DIL may have been less than imaged on the pretreatment MR leading to an overestimation of the ECE at the time of treatment.

We believe that a further refinement of TRUS/MR guided realtime HDR brachytherapy is dose escalation to the Dominant Intraprostatic Lesions (DIL) using dose painting and inverse planning. Consequently, we have started a phase II clinical trial investigating the feasibility and safety of this dose escalation (NCT01909388). A similar clinical trial is ongoing in British Columbia, Canada (NCT01605097). For the ongoing trial, we have modified our approach to include a second MR, acquired the same day as the HDR procedure using a Foley catheter and a 2.5 cm diameter rectal cylinder to mimic the ultrasound probe. Results from well-designed clinical trials will elucidate whether better coverage of the ECE or local dose escalation to the DIL will produce improved disease control without increasing normal tissue complications.

MR imaging contributes significant incremental value to the nomograms for the prediction of ECE, and is by far the best imaging technique for prostate cancer staging. We recommend MR staging for high risk patients prior to HDR brachytherapy and incorporation of this information into the dosimetric planning process. Although, MR-guided HDR is not likely to be readily available in the near future, real-time TRUS/MR fusion can accomplish the same goal with currently available equipment and software.

Disclosure

Authors report no conflict of interest.

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