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Pulsed-dose rate brachytherapy in prostate cancer

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Publication date
2010

[Link to publication](#)

Citation for published version (APA):

Pieters, B. R. (2010). *Pulsed-dose rate brachytherapy in prostate cancer*. [Thesis, fully internal, Universiteit van Amsterdam].

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**CONTRAST-ENHANCED ULTRASOUND AS SUPPORT
FOR PROSTATE BRACHYTHERAPY TREATMENT PLANNING**

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Submitted

ABSTRACT

Background and Purpose. To investigate the possibility for localization of intraprostatic lesions (IL) with contrast-enhanced ultrasound (CEUS) to support the brachytherapy treatment planning of temporary implants.

Material and Methods. Two brachytherapy treatment plans were generated for 8 patients treated with external beam radiotherapy and pulsed-dose rate brachytherapy boost for prostate cancer. The first and second brachytherapy treatment plan was without and with knowledge of the localization of the ILs, respectively. Pairwise comparison was performed on prostate, rectum, and urethra dose-volume parameters and total reference air kerma (TRAK)-values.

Results. Coverage of the ILs by the 140% isodose was increased from mean 66.0%-67.7% for the standard plan to mean 92.5%-95.7% for the adapted plan. The mean D90 of the ILs increased from 1.49-1.57 Gy/pulse to 1.76-1.81 Gy/pulse. Dose-volume parameters for the prostate, rectum, and urethra and the TRAK did not change.

Conclusion. CEUS technique is a promising method for IL localization to aid in brachytherapy treatment planning. Dose coverage on the IL could be improved without increase of dose in organs at risk.

INTRODUCTION

Histologic examination of the prostate harboring a malignancy often reveals multiple areas with malignant lesions. [1]. These malignant lesions differ in size and morphologic appearance and can be divided in dominant lesions and smaller insignificant lesions [2, 3].

If radiotherapy is used for treatment it is common practice to treat the whole prostate. In general the dose to the prostate is evenly distributed with the same dose applied to malignant lesions as healthy prostate areas. Van Lin et al. proposed to better identify dominant intraprostatic lesions (DILs) in order to treat the entire prostate to a moderate dose and giving a boost on these DILs [4].

To apply a boost dose to DILs imaging techniques are needed to identify these areas. Several techniques are reported able to identify tumor lesions within the prostate [5, 6]. One of these techniques is Magnetic Resonance Imaging (MRI). T2-weighted imaging (T2-WI) provides a morphological localization of tumor lesions. T2-WI can be combined with functional imaging for additional information on tumor presence. For the purpose of functional imaging dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted imaging (DWI), and magnetic spectroscopic imaging (MRSI) can be used.

Positron emission tomography (PET) lack the high spatial resolution MRI has. Combination of PET with computer tomography (CT) offers better depiction of tumor areas within the prostate. Promising radiotracers are carbon-11 (^{11}C -choline and ^{11}C -acetate) and fluoro-18 (^{18}F -fluorocholine and ^{18}F -fluoroacetate).

Another modality to visualize tumor lesions is with ultrasound (US) imaging. Particularly contrast-enhanced ultrasound (CEUS) imaging has the ability to detect these lesions [7]. This technique visualizes perfusion within the prostate. Because of increased microvessel density in tumor areas discrimination with healthy prostate tissue is obtained. US contrast is provided by small encapsulated intravenously injected gas bubbles, which behave as additional reflectors in the blood stream. In a correlation study with prostatectomy specimens Sedelaar et al. found contrast-enhanced power Doppler ultrasonography able to find up to 79% of lesions larger than 5-mm [8]. Modern contrast imaging technique uses the non-linear behavior of the microbubbles to increase selective imaging of the bubbles for tumor detection [9].

Modern transperineal prostate brachytherapy is in general performed with US guidance. Brachytherapy is characterized by a heterogeneous dose distribution and it should be possible to treat the whole prostate gland to an elective dose with a boost on macroscopic tumor areas. The aim of this study was to investigate if CEUS techniques can support in brachytherapy treatment planning.

METHODS AND MATERIALS

Ten patients with prostate cancer who underwent external beam radiotherapy with pulsed-dose rate (PDR) brachytherapy were entered in this study. The study is registered with www.clinicaltrials.gov.

trialregister.nl (number NTR1168). Details of the treatment were previously reported [10, 11]. In brief patients were treated on the prostate and base of the seminal vesicles with 3-dimensional conformal external beam radiotherapy to deliver a dose of 46 Gy in daily 2 Gy fractions. Subsequently within 1 week a transperineal implantation was performed with flexible catheters for PDR brachytherapy. The Oncentra Prostate planning system (Nucletron B.V., Veenendaal, The Netherlands), was used for intra-operative treatment planning. Catheter positions were determined for a provisional treatment planning. Definitive treatment planning was done with CT-scan without the rectal US probe to equal at best the treatment situation. The brachytherapy prescribed dose on the planning target volume (PTV) was 28.8 Gy in 1.2 Gy pulses and a period time of 2.0 hours between pulses. The PTV was defined as the prostate gland without margin.

CEUS image processing and identification of intraprostatic lesions

Prior to start of treatment the patients underwent an examination with CEUS. The sulphur hexafluoride microbubbles (Sonovue™ from Bracco, Milan, Italy) were intravenously injected via the antecubital fossa.

US imaging was performed using an iU22 US scanner (Philips Healthcare, Bothel, USA) and a C8-4v probe. The power modulation technique was used for CEUS imaging. All imaging sequences were stored in the DICOM format, and transferred to a personal computer for further analysis. Off-line, the intraprostatic lesions in the CEUS sequences were delineated. The lesions were identified in the peripheral zone only, by vision inspection of fast and/or increased enhancement. In total 2 boluses of 2.4 ml contrast were injected, and the inflow of contrast was judged. During up to 4 minutes after the injection additional planes were examined using the destruction-replenishment technique. In this manner, the whole prostate was examined for suspected lesions.

Imaging was performed and stored in the transverse orientation with a continue grayscale sweep from base to apex, together with one longitudinal maximum cross-section. Using correlation techniques, we were able to correlate each plane in the transverse sweep to one location in the longitudinal sweep and a 3-dimensional (3-D) reconstruction of the prostate was made. Each CEUS recording in a transverse plane was search for in the recorded sweep, and therefore the location of each CEUS recording could be reconstructed into the 3-D data-set. The delineated lesions were drawn in this 3-D data-set, and the result was used for the fusion with the planning system imaging data-set.

Image fusion

The US images used for brachytherapy planning were acquired using a 2-D side viewing US probe which position was controlled by a stepper. The images have a resolution of 0.4 x 0.4 mm² in-plane with 1 mm slice separation.

The brachytherapy planning images were combined into a 3-D volume and registered to the 3D reconstructed US scan as described above. This data-set has 0.17 x 0.17 x

0.17 mm³ voxels. Besides the reconstructed US scan, a corresponding 3-D data-set was available in which the CEUS detected IL is indicated as binary mask. All 3 data-sets were loaded into a in-house software system for image registration and fusion [12]. The software was extended with a rigid registration method suitable for US-US registration similar to the method proposed by Roche et al [13]. First, both US images were manually aligned for translation and rotation in 3-D (6 degrees of freedom). During this step both US data-sets were visualized in 3 orientations (transverse, sagittal and coronal) and overlaid in a green-purple color wash or as an interactive cut display. Then, the US volumes were processed by an unsharp mask filter to extract gradient information. The final registration is performed by optimizing the correlation ratio metric between both processed US data-sets. Both for visualization and registration the US scans were resampled using trilinear interpolation. The registration accuracy was mainly limited by differences in deformation between both US data-sets because of difference in applied probe pressure. From the visual verification the registration accuracy is estimated to be better than 2 mm. After approval of the registration, the binary volume was overlaid on the brachytherapy US using the 3-D translation and rotation obtained from the US registration.

A new treatment plan was created on the fused images. Treatment planning was performed with the Oncentra Prostate planning system. For each patient two plans were generated. The first plan without and the second plan with the intraprostatic lesions (IL) visualized.

Dose constraints were formulated for the first treatment plan. The prostate volume covered by the reference dose (RD) should be 95% or more ($V_{100-p} \geq 95\%$), the minimal dose to the 2 ml rectal volume receiving the highest dose should be 0.97 Gy/pulse or less ($D_{2ml-r} \leq 0.97$ Gy/pulse), the maximum urethral dose (D_{max-u}) should be 140% RD (1.68 Gy/pulse).

The second treatment plan was created with the above-mentioned constraints and an additional constraint prescribing at least 95% of the IL volume covered by the 140% RD ($V_{140-il} \geq 95\%$).

The brachytherapy treatment plans with and without US contrast were compared to each other. Cumulative dose-volume histograms (DVH) were calculated and compared. DVH-parameters used for comparison were V_{100-p} , V_{150-p} , D_{90-p} , D_{2ml-r} , D_{max-u} , and total reference air kerma at 1 m (TRAK).

Statistics

Pairwise comparison of the means of the DVH-parameters was done by the Wilcoxon signed rank sum test. All tests were two-sided, and P-values <0.05 were considered significant. Statistical analysis was performed with the Predictive Analytics SoftWare Statistics, version 18.0 for Mac OS X (PASW 18.0, Chicago, IL, USA).

Table 1. Intraprostatic lesions (IL) characteristics.

Prostate volume		Median 35.90 ml	Range 16.80-50.20
Number of IL's	1	4	
	2	4	
Extraprostatic extension	Yes	6	
	No	6	
Volume IL1		Median 0.25 ml	Range 0.04-0.53
Volume IL2		Median 0.09 ml	Range 0.03-0.18
Size IL1		Median 12.90 mm	Range 6.00-18.10
Size IL2		Median 8.50 mm	Range 5.90-11.00

RESULTS

One patient did not show ILs on CEUS and for another patient fusion of CEUS-images on the brachytherapy treatment planning images was not possible due to large variation in prostate shape of the two studies. These two patients were excluded from further analysis. The median prostate volume was 35.90 ml (range 16.80-50.20). Four patients had only 1 IL and the other 4 had 2 ILs at both sides of the prostate. The largest of both IL within a prostate was coded as IL1 and the smallest was IL2. Six of these ILs showed extracapsular extension (Table 1).

In Table 2 it is shown that the mean V140 of the ILs was increased from 66.0%-67.7% to 92.5%-95.7%. Also, the mean D90 on the ILs was increased from 1.49-1.57 Gy/pulse to 1.76-1.81 Gy/pulse (Fig. 1). In 6 cases the first treatment planning was performed with 12 catheters and in the other 2 cases 14 catheters were used. In all cases the same number of catheters was used by repositioning the catheters corresponding to the location of the ILs.

The adapted treatment plan did not lead to an alteration of the DVH-parameters of the prostate, rectum, and urethra (Table 3). Also, a statistically non-significant increase of the TRAK was observed.

Table 2. Intraprostatic lesions (IL) mean dose-volume parameters for a non-adapted and an adapted treatment plan

	Non-adapted	Adapted
V140 IL1 (%)	67.70	92.70
D90 IL1 (Gy/pulse)	1.57	1.81
V140 IL2 (%)	66.00	95.70
D90 IL2 (Gy/pulse)	1.49	1.76

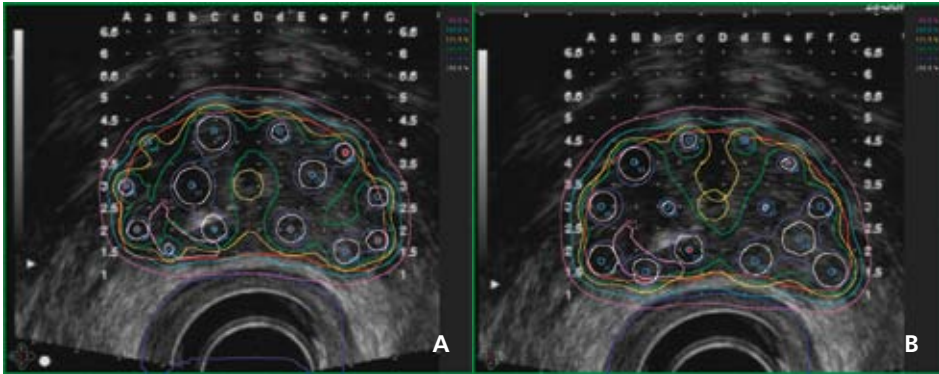


Fig 1. Brachytherapy isodose distribution without (a) and with (b) knowledge of the position of an intraprostatic lesion in the right peripheral zone. Note the coverage of the IL by the 140% isodose.

DISCUSSION

In this pilot study we have investigated the possibility of introducing CEUS data for prostate brachytherapy treatment planning. To our knowledge this is the first study investigating this technique for brachytherapy. It appeared that with knowledge of the position of ILs a better treatment plan could be generated with improved coverage of the ILs in the high dose regions. Better coverage of ILs was achieved by including the intraprostatic part as well as the extraprostatic extension into the high-dose region. The better coverage of the ILs resulted also in a higher dose (D90) in the ILs. In this small study we could not find an alteration in DVH-parameters of the prostate. More important the adapted plans did not lead to higher doses in the rectum and urethra. We have succeeded by just repositioning the catheters to improve the adapted plan. We have not encountered a need for adding more catheters in our study, but that may be necessary in certain situations.

The TRAK was calculated to investigate changes in exposure to radioactivity. A statistically non-significant increase in TRAK was observed in the adapted plans compared

Table 3. Mean dose-volume parameters and TRAK for a non-adapted and an adapted treatment plan

	Non-adapted	Adapted	P-value
V100 prostate (ml)	35.70	35.80	0.40
V150 prostate (ml)	13.70	14.20	0.61
D90 prostate (Gy/pulse)	1.36	1.37	0.61
D2ml rectum (Gy/pulse)	0.84	0.88	0.08
Dmax-u (Gy/pulse)	1.51	1.49	0.06
TRAK (μ Gy at 1 m)	459	473	0.09

to the original plans. Careful attention should be paid in TRAK-values to be informed on exposure to radioactivity, which cannot be found in the prescribed dose or dose coverage to organs. Adaptation of treatment plans can easily lead to large differences in radiation exposure and should be considered in future studies.

The question still remains how accurate is the CEUS technique for identification of tumor lesions in order to introduce this concept with brachytherapy into the clinic. Halpern et al. compared the results of CEUS with 12 prostatectomy specimens [14]. In this small study they found a positive predictive value for tumor identification of 56% and a sensitivity of 42%. These numbers indicate a high false negative rate because tumor lesions are missed.

In a similar study Sedelaar et al. found CEUS investigation by an experienced investigator to have a detection rate of 61% for prostate tumor lesions [8]. However, they also found a detection rate of 79% for large sized (≥ 5 -mm) lesions. The implication for brachytherapy is that at least the large sized tumor areas are identified that probably also need the highest dose.

Van Moerkerk et al. investigated the discriminative value of CEUS investigation for prostate tumor lesions with the Receiver Operator Characteristic [15]. They found an area under the curve of 0.65, meaning that in 65% of the cases the investigation could discriminate between malignant and benign lesions. The discriminative value for dorsal sided lesions was higher than for ventral sided lesions.

In a recent study of Seitz et al. they found a sensitivity of 71.0%, a specificity of 50.0%, a positive predictive value (PPV) of 91.7%, and a negative predictive value (NPV) of 18.2% for detecting prostate cancer on a per-patient basis with CEUS using cadence-contrast pulse sequence technology [16]. With this low specificity and NPV one could question the utility for screening on prostate cancer. However, in the group of patients with demonstrated prostate cancer the CEUS technique has proven to be able to detect the present lesions in a high percentage of cases, especially large sized lesions.

Other means for detecting malignant prostatic lesions with high spatial resolution is with MRI. However, also with MRI tumor lesions can be missed or tumor extension can be misdiagnosed. In a systematic review with meta-analysis Engelbrecht et al. found with ROC-curves a test accuracy for discriminating T2 from T3 tumors of 71% [17]. In this study classification of T-stage was done on a per-prostate level and probably the accuracy on a per-lesion level would have been less. Because in general prostate brachytherapy implantations are performed under US guidance, identification of tumor lesions on US is more advantageous than on MRI. If MRI is used for tumor localization fusion of images must be used if the US technique is used for implantation bringing in another source of geometric uncertainties. New developments in MRI-based implantations may circumvent this problem [18-21].

In our study we used rigid matching for contrast-enhanced images and US images for treatment planning. Because of shape deformation we encountered some difficulties in

fusion of image studies. This uncertainty may question the reliability of this procedure in a clinical setting. For this reason patients were not actually treated with the adaptive plan. However, we have shown as a proof of principle that by identification of tumor lesions within the prostate brachytherapy treatment plans can be adapted for better lesion coverage and no increase of dose in the OAR. CEUS is a promising technique to aid in adaptation of brachytherapy treatment plans. Further developments in deformable image fusion will help in better localization of the ILs. Also, developments for a suitable side-viewing probe to be used for both contrast-enhanced images and transperineal implantations would make this method suitable for clinical usage in prostate brachytherapy.

CONCLUSION

Identification of ILs in the prostate with CEUS can aid in adapting brachytherapy treatment planning for an improved coverage of the ILs without increasing the dose to the OARs. Further developments in image fusion and US hard- and software are needed before introduction into the clinic.

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