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Contrast-enhanced ultrasound as support for prostate brachytherapy treatment planning

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Abstract

Purpose: To investigate the possibility of 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.

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

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Key words: contrast-media, ultrasonography, image-processing, brachytherapy planning, prostate.
microbubbles to increase selective imaging of the bubbles for tumor detection [12]. Although in the early studies on CEUS for prostate cancer detection, low sensitivity and specificity rates were reported, modern ultrasound techniques and quantitative ultrasound imaging are more promising [11,13-15]. The recent reports indicating high accuracy for prostate cancer detection enable the CEUS technique to be used for prostate cancer radiotherapy [16,17]. 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 brachytherapy treatment planning. Since the value of the CEUS technique for routine clinical use has not been determined yet, this study should be considered as a proof of principle for future use.

Material and methods

Ten patients with prostate cancer who underwent external beam radiotherapy with pulsed dose-rate (PDR) brachytherapy were included in this study. The study is registered with www.trialregister.nl (number NTR1168). Details of the treatment were previously reported [18,19]. In brief, patients were treated for 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 a 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 provisional treatment planning. Definitive treatment planning was done with CT-scan without the rectal US probe to closely simulate the actual treatment geometry. The prescribed brachytherapy dose on the planning target volume (PTV) was 28.8 Gy in 1.2 Gy pulses and a 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 with external beam radiotherapy patients underwent an examination with CEUS as an outpatient procedure. The sulphur hexafluoride microbubbles (Sonovue™ from Bracco, Milan, Italy) were injected intravenously via the antecubital fossa. US imaging was performed using an iU22 US probe (Philips Healthcare, Bothel, USA) and a C8-4v endocavity probe. The power modulation technique was used for CEUS imaging. All imaging sequences were stored in the DICOM (Digital Imaging and Communication in Medicine) format, and transferred to a personal computer for further analysis. Off-line, the intraprostatic lesions in the CEUS sequences were delineated. This contouring was done in the transverse plane on areas with a fast or increased enhancement as compared to the main enhancement of the peripheral zone. In total, 2 boluses of 2.4 ml of contrast were injected, and the inflow of contrast was monitored. 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 continuous grayscale sweep from base to apex, together with one longitudinal maximum cross-section. The midline of each frame in the transverse sweep is also located in the longitudinal cross-section. Using correlation techniques we were able to correlate each plane in the transverse sweep to one location in the longitudinal cross-section, and 3-dimensional (3D) reconstruction of the prostate was made. Each CEUS recording in a transverse plane was searched for in the recorded sweep, and therefore the location of each CEUS recording could be reconstructed into the 3D data set. The delineated lesions were drawn in this 3D 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 2D side viewing US probe which position was controlled by a stepper. The images had a resolution of 0.4 × 0.4 mm² in-plane with 1 mm slice separation. The brachytherapy planning images were combined into a 3D volume and registered to the 3D reconstructed US scan as described above. This data set had 0.17 × 0.17 × 0.17 mm³ voxels. Besides the reconstructed US scan, a corresponding 3D data set was available in which the CEUS detected intraprostatic lesion (IL) was indicated as binary mask. All 3D data sets were loaded into an in-house software system for image registration and fusion [20]. The software was extended with a rigid registration method suitable for US-US registration similar to the method proposed by Roche et al. [21]. First, both US images were manually aligned for 3D translation and rotation (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 was performed by optimizing the correlation ratio metric between both processed US data sets. Both for visualization and registration purposes, 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. For the visual verification the registration accuracy was estimated to be better than 2 mm. After approval of the registration, the binary volume with the delineated ILs was overlaid on the brachytherapy US using the 3D translation and rotation obtained from the US registration (Fig. 1).

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 ILs visualized. Dose constraints were formulated for the first treatment plan. The prostate volume covered by the reference dose (RD) should be 95% or more (V100-p ≥ 95%), the minimal dose to the 2 ml rectal volume receiving the highest dose should be 0.97 Gy/pulse or less (D2ml-r ≤ 0.97 Gy/
pulse), the maximum urethral dose (Dmax-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 (V140-il ≥ 95%) (Fig. 2).

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 V100-p, V150-p, D90-p, D2ml-r, Dmax-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).

**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 a large variation in the prostate shape of the two studies. These two patients were excluded from further analysis. The median prostate volume was 35.9 ml (range 16.8-50.2). Four patients had only 1 IL and the other 4 had 2 ILs at both sides of the prostate. The largest of both ILs within a prostate was coded as IL1 and the smallest – as IL2. Six of these ILs showed extracapsular extension (Table 1).

Table 2 shows that the mean V140 of the ILs was increased from 66.0-67.7% to 92.5-95.7%. Also, the mean D90 on
Significant increase of the TRAK was observed (Lead to an alteration of the DVH-parameters of the prostate, the location of the ILs. The adapted treatment plan did not heters were used. In all cases the same number of catheters performed with 12 catheters and in the other 2 cases, 14 cat -

In this pilot study we have investigated the possibility introducing the 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 only 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 [11]. 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, clinically significant lesions, are identified. These high-volume tumor bearing areas probably need the highest dose [22].

A new development in the use of CEUS for prostate cancer detection is the ultrasound signal analysis and its quantification. The aim is to make the analysis less subjective and to increase the accuracy for tumor detection. At the Eindhoven University of Technology and Academic Medical Center, a diffusion parameter was investigated and compared to prostatectomy specimens [17]. A high sensitivity (81.2%) and specificity (84.6%) value was found for prostate cancer detection. Also the ROC area (Receiver Operating Characteristic area) under the curve was as high as 0.909. This finding is very promising and needs further investigation. Other means of detecting malignant prostatic lesions with high spatial resolution is the use of MRI. However, also with the use of MRI tumor lesions can be missed or tumor extension can be misdiagnosed. In a systematic review with meta-analysis Engelbrecht et al. found, using ROC-curves, a test accuracy for discriminating T2 from T3 tumors of 71%
In this study, a classification of T-stage was done on a per-prostate level and probably the accuracy on a per-
leison level would have been lower. At a European consen-
sus meeting, there was a large disagreement between ex-
erts in the field on how to use mpMRI for prostate cancer
imaging [7]. Consensus was reached on 67% of items related
to imaging parameters for tumor detection and localization,
and on only 54% of items related to imaging interpretation
and reporting. So, even for the more clinically used imaging
 technique of MRI, as compared to CEUS, further in-
vestigation should be performed as to its validity. It is ex-
pected that both imaging techniques will play a major role
in the future for image guided and targeted radiotherapy
[24]. Because in general prostate brachytherapy, implan-
tations are performed under US guidance, identification
of tumor lesions on US is more advantageous than on MRI.
If MRI is used for tumor localization purposes, fusion of im-
ages must be used if the US technique is used for implant-
ing bringing in another source of geometric uncertain-
ties. New developments in MRI-based implantations may
circumvent this problem [25-28].

In our study we used rigid matching for contrast-en-
hanced images and US images for treatment planning.
Because of shape deformation we encountered some diffi-
culties in fusion of image studies. This uncertainty may ques-
tion 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 prin-
ciple that by identification of tumor lesions within the
prostate brachytherapy treatment plans can be adapted for
better lesion coverage without any increase of dose in the
OAR. CEUS is a promising technique to aid in adaptation of
brachytherapy treatment plans. For practical clinical us-
age a suitable side-viewing probe should be developed for
both contrast-enhanced images and transperineal implant-
ations. After analysis of the images, contouring of the pro-
state and ILs is performed for brachytherapy planning. This
way implantation is performed without the need for image
fusion. Without such a dedicated probe, deformable image
fusion techniques are absolutely needed for proper local-
ization and positioning. When the treatment planning is
done the implantation can be performed according to the
plan and needle placement in the vicinity of the ILs.

Conclusions

Identification of ILs in the prostate with CEUS can help with 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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