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Prostate radiotherapy

Difficulties and potential of correlating local recurrences in prostate cancer with the delivered local dose

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ABSTRACT

In the previous decades the distinction between a local relapse and distant metastases was difficult to accomplish in an early stage. As a consequence, a failure could only be coarsely related to the original radiotherapy treatment. Currently, due to better imaging and position verification techniques, the actual dose within the prostate can be estimated, taking position uncertainties into account. Furthermore, advanced functional MRI techniques, such as MR spectroscopy (MRS) and dynamic contrast-enhanced MRI (DCE-MRI), increase the chance of localizing a local recurrence within the prostate. With this information the correlation between the actual previously delivered dose and a local relapse can be established, using non-rigid registration of the planning CT and the post-recurrence MRI. The current study describes the possibilities and problems in obtaining this correlation. This serves as a framework for investigating a reliable dose effect relationship in the future.

Prostate cancer is the most common malignancy in men in both North America and Europe and plays an important role in cancer death. In an early stage, locally confined disease can be cured by radiotherapy [1]. Nevertheless, a significant number of patients suffer from a biochemical relapse during follow-up. In the previous decades it was difficult to distinguish between locally recurrent disease and distant metastases when the prostate specific antigen (PSA) level increased following primary treatment. Still many of these patients will harbour organ-confined disease [26]. As a consequence, a failure could only be coarsely related to the original radiotherapy treatment. From the recent dose escalation trials it has become clear that a treatment with a higher dose to the prostate decreases the likelihood of a PSA relapse [2,3]. Yet, it remains unclear if the failures in either treatment arm are located inside the volume that received the nominal dose, at the edges or at a distance. Thus it is difficult to establish what should be the next step to improve the treatment.

Several studies use advanced MR imaging techniques to identify the location of a recurrence of residual tumor after a PSA relapse [4–8]. In particular MR spectroscopy (MRS) and dynamic contrast-enhanced (DCE-) MRI show a high accuracy in detecting a local recurrence in the prostate [5,7–9]. Although the number of patients in these studies is fairly small, and pre-treatment imaging data are incomplete, it appears that a local recurrence after radiotherapy mainly occurs at the area of the primary dominant intraprostatic lesion (DIL) [4,6]. With such imaging data it becomes feasible to establish a much more detailed relation between failure and the dose distribution of the original treatment. A failure at the site of the original tumor (a Gross Tumor Volume (GTV)-recurrence) suggests that insufficient dose has been given to the DIL, i.e. the GTV. A failure in the prostate at another location than at the DIL (a Clinical Target Volume (CTV)-recurrence) suggests that subclinical disease received insufficient dose. Failure at the edge of the treatment field may also be indicative of positioning errors, so that the planned dose was not actually delivered.

In this study, we explore the difficulties and potential of relating the location of a recurrence to the originally delivered dose. We included 14 patients presenting with a PSA relapse at least 25 months after initial treatment with either conformal radiotherapy, IMRT or I-125 brachytherapy. An MRI examination was done containing T2-weighted and DCE-MRI sequences. Also, we derived the dose that was delivered at the site of the recurrence. In patients treated with I-125 brachytherapy, the dose was delivered from the postplanning CT scan, made 4 weeks after implantation. For patients treated with IMRT and daily fiducial gold-marker-based position verification we re-calculated the dose delivered to the prostate taking position variations into account. For patients treated with conformal radiotherapy, without precise position verification we determined the minimal distance of the recurrence to the 95% isodose of the original treatment plan.

We believe that with this approach it will become possible to identify a dose effect relation for both the dominant lesion and subclinical disease in prostate cancer. The study describes the current possibilities and problems in achieving this correlation.

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Materials and methods

Patients

At the department of radiotherapy in the UMC Utrecht DCE-MRI imaging has been performed on 14 patients with a biochemical failure according to the Phoenix definition (nadir + 2 ng/ml) [22] after primary radiotherapy. These patients were treated by I-125 brachytherapy ($n = 8$) or EBRT ($n = 6$). Patient characteristics, treatment type, year of treatment and relapse characteristics are described in Table 1.

I-125 brachytherapy was performed under transrectal ultrasound guidance, using a template. All needles were inserted transperineally. The position of the needles was verified by 3D transrectal ultrasound and stranded or loose seeds were introduced to reach a dose to the prostate of 144 Gy. CT scans were made 1 day as well as 4 weeks after treatment. Because approximately 25 days is considered the optimal time for calculation of the dose [19], the latter was used for postplanning. The used techniques are described in detail in Battermann et al. [14].

Of the 6 patients receiving external beam radiotherapy, 3 patients received intensity-modulated radiotherapy (IMRT) to a dose of 76 Gy in 35 fractions, using a simultaneous integrated boost [10]. A margin of 8 mm was used for the PTV around the prostate and seminal vesicles as delineated on CT. Daily off-line position verification with an adapted Shrinking-Action Level protocol was performed using gold-fiducial markers [11–13]. In our clinic, this resulted in a reduction of systematic set-up errors to $\Sigma = 0.8$ mm. [12], so that the planned dose to the prostate and the actual dose showed negligible differences [27]. The three other patients were treated before the introduction of dose escalation in our clinic, with a conformal technique to a dose of 70 Gy in 35 fractions. A 3-field technique was applied, with a margin of 8 mm for the Planning Target Volume (PTV) around the prostate and seminal vesicles as delineated on CT. For these patients position verification was done only with a megavoltage photo in the first week of treatment, registering the bony anatomy. As the correlation between the position of the prostate and the bony anatomy is weak [28], the systematic set-up error lies in the same range as when no correction would have been applied. This is 2.2 mm in the lateral direction, 2.9 mm in the longitudinal direction and 4.8 mm in the vertical direction [12].

MRI examination after biochemical relapse

No patient received any hormonal therapy prior to the DCE-MRI

All patients in this study underwent an MRI examination on a 3 Tesla MRI scanner (Achieva Phillips Medical Systems, Best, The Netherlands), using a SENSE cardiac coil with 6 elements. A T2-weighted TSE scan (TR/TE 8400/120 ms) was made with 25 slices of 4 mm, FOV 20 × 20 cm, acquisition matrix and reconstruction matrix 256 × 256. Also a balanced Turbo Field Echo (TFE) scan was made with SPAIR fat suppression (TR/TE 2.8/1.4 ms, 90 slices of 1 mm, FOV 25 × 25 cm, acquisition matrix 192 × 249, reconstruction matrix 512 × 512). This sequence is not common in a diagnostic setting, but it is part of our routine protocol and used for delineation of the entire gland because of its high spatial resolution. In this study, we use it to register the MRI images to the planning CT scans.

The dynamic contrast-enhanced (DCE) protocol consisted of a 3D spoiled gradient echo sequence (TR/TE = 4.0/1.0 ms, flip angle 8°). A total of 120 acquisitions were acquired every 2.4 s. A single acquisition consisted of 20 axial slices of 2.5 mm. The FOV was 40 × 40 cm, acquisition matrix 128 × 128, reconstruction matrix 160 × 160. After three acquisitions, 0.1 ml/kg body weight gadolinium DTPA (1.0 M) (Gadovist, Schering) was administered at an injection rate of 2.0 ml/s, followed by a saline flush. Signal intensity variations were converted to changes in contrast agent concentration by using estimates of the pre-contrast T1 relaxation time, which was mapped before administration using the variable multi flip angle method.

Tracer-kinetics modeling was done using the Tofts model [15] resulting in 3D maps of the transfer constant K^{trans}, the extravascular extracellular space (EES) fractional volume v_e and the rate constant k_{ep}. A standardized arterial input function was used, based on the average of 50 patients scanned with the same protocol. The delay between input function and onset of enhancement in the prostate was fitted individually [24]. Areas were identified with low signal intensity on T2-weighted images and increased values of K^{trans}. Rouviere et al. [5] showed high sensitivity and specificity of this approach in the peripheral zone of the prostate. However, in the central gland, high values of K^{trans} may be found around the urethra and in the presence of benign prostate hypertrophy (BPH), reducing the specificity of the examination.

For patients treated with I-125 brachytherapy, the seeds are visible in the T2-weighted MRIs as small dark spots. On the K^{trans} maps their impact is not visible.

Biopsies

If indicated as positive by the MRI examination, patients were referred to the urologist for biopsies. Although high values of K^{trans} in the central gland may be false positives, we did refer these cases for biopsy as well. Patients with a negative MRI examination were not referred.

Table 1
Patient characteristics. PSA = prostate specific antigen, DCE-MRI = dynamic contrast-enhanced MRI, for DCE-MRI and biopsy outcome: positive = 1/negative = 0/n.a. = not available, IMRT = intensity-modulated radiotherapy. D95 (*): for I-125 the D95 of the corpus is listed, not of the prostate including seminal vesicles.

Patient	Age [year]	Initial PSA [ng/ml]	T stage	Grade	Gleason Sum	Primary therapy	Prostate D95 (*)	PSA Nadir [ng/ml]	Interval nadir [months]	PSA at DCE-MRI [ng/ml]	MR interval [months]	DCE-MRI outcome	Biopsy outcome
1	51.7	3.3	1c	1	6	I-125	71.5	0.7	12.0	3.5	55	1	1
2	51.5	5.0	2a	1	6	I-125	117.1	0.2	24.3	1.5	58	1	1
3	66.5	6.5	1	2	7	I-125	129.6	2	5.9	2.2	79	0	n.a.
4	68.0	4.8	2	1	5	I-125	70.5	3	3.1	6.6	25	1	0
5	65.8	5.7	2b	2	7	I-125	149.0	1	12.1	5.5	37	0	n.a.
6	64.8	11.5	2	2	7	I-125	132.6	1	7.6	4.8	69	0	n.a.
7	63.1	13.0	1c	1	5	I-125	91.5	0.6	54.3	4.4	85	1	0
8	71.4	17.0	1c	2	7	I-125	48.8	0	1.2	2.9	48	1	1
9	69.5	33.0	3	2	7	IMRT	70.5	0.2	8.8	n.a.	36	1	0
10	67.8	7.2	3	2	7	IMRT	74.8	1	8.4	4	32	1	1
11	76.1	n.a.	3	2	7	IMRT	68.4	3.2	13.9	6.4	38	0	n.a.
12	66.2	62.5	3	2	7	Conformal	65.9	0.8	38.9	2.1	82	1	n.a.
13	67.2	22.8	3	2	7	Conformal	68.5	0.6	12.0	2.8	64	1	0
14	62.1	13.0	3a	1	6	Conformal	63.4	0.6	21.1	n.a.	85	1	1