Magnetic resonance imaging for prostate cancer radiotherapy

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ABSTRACT

For radiotherapy of prostate cancer, MRI is used increasingly for delineation of the prostate gland. For focal treatment of low-risk prostate cancer or focal dose escalation for intermediate and high-risk cancer, delineation of the tumor is also required. While multi-parametric MRI is well established for detection of tumors and for staging of the disease, delineation of the tumor inside the prostate is not common practice.

Guidelines, such as the PI-RADS classification, exist for tumor detection and staging, but no such guidelines are available for tumor delineation. Indeed, interobserver studies show substantial variation in tumor contours. Computer-aided tumor detection and delineation may help improve the robustness of the interpretation of multi-parametric MRI data. Comparing the performance of an earlier developed model for tumor segmentation with expert delineations, we found a significant correlation between tumor probability in a voxel and the number of experts identifying this voxel as tumor. This suggests that the model agrees with ‘the wisdom of the crowd’, and thus could serve as a reference for individual physicians in their decision making.

With multi-parametric MRI it becomes feasible to revisit the GTV-CTV concept in radiotherapy of prostate cancer. While detection of index lesions is quite reliable, contouring variability and the low sensitivity to small lesions suggest that the remainder of the prostate should be treated as CTV. Clinical trials that investigate the options for dose differentiation, for example with dose escalation to the visible tumor or dose reduction to the CTV, are therefore warranted.

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Introduction

Radiotherapy for prostate cancer has been proven an effective form of treatment and is to date one of the standard treatment options available. The current practice is to treat the entire prostate with a more or less homogeneous dose. This is remarkable, as it is well known that tumors are distributed inhomogeneously inside the prostate. Already in 2000, Chen et al. [1] showed in 180 prostatectomy specimens that 74% of the cancer foci were located in the peripheral zone. In 83% of patients, more than one tumor focus was found. Hollmann et al. [2] showed in 61 prostatectomy specimens that the index lesions, defined as the largest tumor inside a prostate, accounted for 88% of the total tumor volume. The contribution of tumor foci < 0.1 cm³ to the total tumor volume was 2%. Ou et al. [3] constructed statistical atlases of the presence of prostate cancer based on 83 prostatectomy specimens, showing the probability of finding a tumor at a particular location.

Multi-parametric MRI (mp-MRI) is now well established for detection of tumors inside the prostate gland and staging of the disease [4–6]. For tumor detection, a protocol consisting of T2-weighted MRI, diffusion-weighted MRI (DWI) and Dynamic Contrast-Enhanced (DCE-) MRI is recommended [7,8]. The recently published Prostate Imaging – Reporting And Data System (PI-RADS) version 2 [9,10] is designed to improve detection, localization, characterization, and risk stratification in patients with suspected cancer in treatment naïve prostate glands.

In radiotherapy, the contouring of the prostate gland is usually based on CT images as planning CT scans form the basis for dose calculations. However, as MRI-based contouring resulted in a smaller target volumes [11], this is now used increasingly for delineation of the prostate gland. Image registration between MRI and planning CT scan is required, unless Hounsfield unit images can be derived from the MR images directly [12,13]. Traditionally, the entire prostate is treated with a more or less homogeneous dose. To improve the therapeutic window between tumor control and toxicity, for low-risk patients, focal treatment options are now considered. For

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intermediate and high-risk patients a focal dose escalation approach can deliver an extremely high dose to the tumor while satisfying dose constraints to normal tissue.

Delineation of the tumor and differentiation of the radiation dose between MRI-visible tumor (Gross target volume, GTV) and the remainder of the gland (Clinical target volume, CTV) is not standard practice [14]. Nevertheless, several planning studies showed the potential for dose escalation to the MRI-visible tumor with external-beam radiotherapy [15,16]. Rylander et al. [17] showed that a combination of dose escalation to the tumor, combined with a de-escalation of the dose to the remainder of the gland is feasible with 125-Iodine seed implant brachytherapy. Two phase III randomized trials investigate the clinical benefit of focal escalation of the dose to the tumor as defined on mp-MRI (FLAME (NCT01168479)) [18], HEIGHT (NCT01411332), but clinical results are as yet not available.

We here review the use of MRI in a diagnostic setting, for staging and tumor detection. We then evaluate how MRI is used for target delineation for radiotherapy. As target delineation is one of the critical steps in the radiotherapy chain, automatic segmentation of images has received increasing interest. For tumors inside the prostate, computer-aided tumor detection is an exciting development that may improve the quality and consistency of interpretation of mp-MRI.

In this study, we therefore also apply our earlier developed model for tumor segmentation [19] to the group of patients that was used in our recent study of interobserver variability [20]. This allows us to establish the quality of the model results relative to the manual segmentations and evaluate its potential for improving tumor delineation consistency.

**MRI for prostate cancer staging and tumor detection**

The use of functional MRI techniques in combination with T2-weighted MRI has been reviewed extensively [4-6]. DWI reflects tissue cellularity and membrane integrity and is quantified by the Apparent Diffusion Coefficient (ADC), representing the diffusion coefficient of water molecules in the tissue. DCE-MRI reflects microvessel density and permeability. The data can be quantified using tracer kinetics modeling. The most commonly used model is the Tofts model [21] that yields the transfer constant Ktrans, representing blood flow and permeability. MR Spectroscopic Imaging (MRSI) shows the relative concentrations of metabolites in cancerous and normal prostate tissue.

Combining T2-weighted MRI, DWI and DCE-MRI, Tanimoto et al. [22] found an area under the receiver operating curve (AUC) for the detection of prostate cancer of 0.966. Reinsberg et al. [23] combined choline/citrate ratios obtained from MRSI with ADC values from DWI and found an AUC of 0.98 when considering voxels positive when containing more than 70% tumor. Isebaert et al. [24] found that DWI had the highest accuracy for tumor localization compared to T2w and DCE-MRI, with more aggressive or more advanced tumors being more easily detected. Significantly higher sensitivities were obtained for the combination of T2w, DCE, and DWI as compared to each modality alone or any combination of two modalities.

A confounding factor in tumor detection with mp-MRI, particularly when using T2w and DCE imaging, is the presence of post-biopsy hematoma. To minimize this effect in a diagnostic setting, MRI scans are usually made at least 6 weeks after biopsies were taken. However, patients scheduled for treatment with radiotherapy often have fiducial markers implanted for position verification during external-beam radiotherapy [25]. As the implantation of these fiducial markers also may cause hematoma, it is relevant to include a T1-weighted sequence in the MRI exam which visualizes hematoma as hyperintense areas inside the prostate gland.

Recently, an expert panel of the European Society of Urogenital Radiology (ESUR), acknowledging that true evidence-based guidelines could not be formulated, presented minimum and optimum requirements [7] as did Dickinson et al. [8], specifying each sequence in detail. For tumor detection, a protocol consisting of T2-weighted MRI, DWI and DCE-MRI is recommended. MR spectroscopic imaging is considered optional.

An important element in the ESUR consensus paper is the PI-RADS. This provides a structured reporting scheme, where for each of the imaging modalities score criteria are defined that reflect aspects that relate to the presence of cancer. The combined scores are summarized in a single PI-RADS score, identifying from 1 to 5 the likelihood of cancer presence [7]. In the recently updated (PI-RADS version 2) [9,10], different parameter scores are no longer added, but instead priorities are given to the different parameters. For the peripheral zone, the deciding factor in the overall score is determined by DWI. For the transition zone, this is T2-weighted Imaging. As DCE-MRI in the transition zone can also reflect benign prostate hyperplasia, its role has diminished.

There are some data on the detection limit of MRI techniques. Schmücking et al. [26] showed that for DCE-MRI, lesions smaller than 3 mm and/or containing less than 30% cancer cells were not detected. For MRSI, the cut-off level was 4 mm and/or less than 40% tumor cell content. Langer et al. [27] found in a study of T2-weighted MRI and DWI that tumors with more than 50% of the area occupied by normal peripheral zone tissue, exhibited T2 and ADC values similar to normal tissue. Thus, the detectability of a lesion depends on both its size and relative tumor content. Turkbey et al. [28] showed a reduced sensitivity and specificity of tumor detection for lesions smaller than 5 mm and with a Gleason score 7 or less. The impact on delineation accuracy is however unclear.

Several studies showed that a low ADC value is associated with a higher Gleason score [29,30]. Somford et al. [31] found that DWI predicts the presence of high-grade tumor in patients with Gleason <6 on biopsies. This suggests that DWI is particularly suitable to detect the more aggressive tumors [32]. Androgen deprivation therapy (ADT) has also been shown to reduce tumor conspicuity on MRI [33]. This is relevant for patients who after their initial diagnosis started with ADT before their referral to a radiotherapy department.

Overall, we can conclude that mp-MRI is well established in the diagnostic setting. Guidelines are now available for acquisition of the data and the PI-RADS system provides a framework for systematic reporting, that reflects the certainty about tumor presence. Chang et al. [34] showed in a retrospective study of 115 patients that inclusion of MRI staging information improved incorporation of extracapsular extension and seminal vesicle invasion in the target in 20% of the patients. Thus, MRI scans can significantly change decisions about target coverage in radical radiotherapy for prostate cancer.

**Multi-parametric MRI for delineation of GTV and CTV**

In contrast to the diagnostic practice, delineation of the CTV (prostate with or without seminal vesicles) in radiotherapy is mostly based on CT for external-beam radiotherapy and ultrasound for brachytherapy. On CT, large inter-observer variations were found particularly at the base and apex of the prostate and around the seminal vesicles [35]. MRI is superior to CT for localization of the prostatic apex [36]. Rasch et al. [11,37] found that on CT, a 1.4 times larger volume was delineated as prostate than on MRI, but no significant differences in interobserver variability were found. To help radiation oncologists to use T2-weighted MRI in combination with CT for target delineation, Villeirs et al. [38] described some key radiologic landmarks that can improve treatment planning, by offering
a clear depiction of the prosatic capsule separating the CTV from the rectum and levator ani muscle, the fibromuscular stroma anteriorly and the transition from normal peripheral zone to fibromuscular tissue caudally. Recently, Sander et al. [39] studied toxicity in 72 patients with CT-based delineations and 73 patients with MRI based delineations prior to radiotherapy. The smaller CTV volume resulting from MRI delineation leads to significantly lower urinary frequency and urinary retention toxicity scores. However, no significant differences in overall urinary or rectal toxicity were found between the two groups.

While MRI helps reduce the volume of delineated target structures, and improves coverage of extracapsular extension and seminal vesicle invasion, the key advantage of MRI lies in the visualization of tumors inside the prostate gland. Here, the same sequences are used as for diagnostic MRI. Whereas a high level of expertise is required for staging and tumor localization, this is even more so for delineation of the GTV where the boundaries of the tumor need to be defined. Unfortunately, to date no guidelines are available about using mp-MRI for tumor delineations. Indeed, large variations in tumor delineations are reported, with kappa values for region-based tumor detection ranging from 0.40 to 0.63 [40,41].

In a study of 5 patients, the voxel-by-voxel kappa value, indicating the intra-observer agreement between 5 observers, ranged from 0.22 to 0.73 [42]. Anwar et al. [43] compared delineations by two observers on T2w imaging and MR spectroscopy with delineations on histology and found these to differ by a median distance of 1.4 mm.

Recently, we studied the agreement between tumor delineations by 6 teams of radiation oncologists and radiologists from 3 centers, and validated this with whole mount histopathology specimens [20]. For 20 patients, 18 index lesions were consistently identified by all observers. The kappa indices for the agreement between the delineations of the teams were 0.61 ± 0.19 (mean ± SD) and the inter-observer contour standard deviation, defined as the standard deviation of the perpendicular distance of each observer’s contour relative to a reference, was 2.3 mm. In addition, 66 out of 69 satellites were missed by all observers. In the analysis of clinical studies of focal dose escalation, these uncertainties need to be considered.

**Computer-aided tumor detection and delineation**

To increase the robustness of the interpretation of mp-MRI data, Rouviere et al. [44] showed that simple combinations of shape and signal abnormalities in mp-MRI could be used to stratify the risk of malignancy of focal abnormalities in the prostate. Several alternative methods have been proposed to extract relevant features for each voxel for classification into normal and tumor tissue using basic classifiers such as support vector machines [45] and logistic regression [19,46,47].

Viswanath et al. [48] use texture features such as Gabor wavelet and Haar wavelet transformation extracted from the T2w-MRI scan to represent each voxel. Groenendaal et al. [19] represent each voxel by several local statistics, e.g. minimum, maximum and median of intensities obtained on ADC and Ktrans maps. After logistic regression, the model provides the probability of tumor presence in individual voxels in mp-MRI. Validation with whole-mount section histology in 12 patients showed an area under the curve of 0.89 for voxels in the peripheral zone of the prostate.

Another approach is to detect regions of interest in the prostate using clustering [49]. Vos et al. [50] used a two-step approach based on a combination of features from T2w, T1, pharmacokinetic and ADC maps. Texture features, such as blobness, were also used to improve its performance. Nevertheless, it is hard to distinguish prostate cancer from confounders such as benign prostatic hyperplasia (BPH), post-biopsy hemorrhage, and atrophy [51,52].

**Inter-observer variability and automated tumor delineation**

In clinical practice, usually only one radiation oncologists delineates a tumor. A delineation, essentially, is a binary decision about voxels being part of the tumor or not. A radiologist can use the PI-RADS score to reflect certainty about the detection of a tumor. A similar system for radiotherapy is however not available. Nevertheless, the study of Steenbergen et al. [18] shows substantial inter-observer variation in delineation. Particularly near the boundary of the tumor, the variation in the delineations of the group of observers reflects the uncertainty about defining this boundary.

The question is now how automated methods for tissue classification in terms of tumor probability relate to the variability of tumor delineations of a group of expert observers. To this end, we applied the model developed earlier by Groenendaal et al. [19] to the group of patients used in the tumor delineation study of Steenbergen et al. [20]. The mp-MRI scan consisted of T2-weighted, DWI and DCE-MRI. Details of the scan protocol and quantitative analysis can be found in [20]. In short, ADC maps were calculated using b-values, representing degrees of diffusion weighting, of 0, 50, 100, 500, 750 and 1000 s/mm². For tracer kinetics modeling of the DCE-MRI data, the signal intensities were first converted to gadolinium concentration values [53] using reference T1 values [54]. The extended Tofts model [21] was fitted to the concentration time curves for estimation of the volume transfer constant (Ktrans) using the method by Murase et al. [55] with a population-based arterial input function. Following [19], the Ktrans map was normalized to the median value of Ktrans in the peripheral zone, to account for measurement variability. Also, all of the parametric maps (T2w, ADC, and Ktrans) were resampled to a grid of 2.5 × 2.5 × 2.5 mm³.

A drawback of the model of Groenendaal [19] is that it was trained by considering delineations of tumors on mp-MRI of 87 patients by radiation oncologists as ground truth, rather than histopathology. We therefore took the same model structure, but retrained it on the cohort used in the delineation study, using delineations of the pathologist on hematoxylin-eosin (H&E) stained slides as ground truth. Each H&E stained slide was registered to the corresponding T2w MRI slice by means of a deformable point-based method (Coherent Point Drift) using landmark points which were visible on both images. This resulted in an average error of 2.1 mm (maximum 5 mm) [20]. Then we tested the model performance in a leave-one-out design. To account for registration errors between MRI and the hematoxylin-eosin stained slides, we excluded voxels that were within a band of 2.5 mm around the tumor boundary (1.25 mm inside and 1.25 mm outside the boundary), as indicated by the pathologist. The area under the ROC curve for a voxel-by-voxel analysis of the peripheral zone had a median of 0.87 (range 0.52–0.99) over the whole patient population. AUCs of two patients were not calculated since there was no tumor in the peripheral zone of these patients. An example of the tumor probability derived from mp-MRI is shown in Fig. 1.

The concept of tumor probability should not be confused with cell density. The latter is a histological property indicating the tissue architecture. A higher cell density (cellularity) can be detected with diffusion-weighted MRI and is associated with cancer. The tumor probability is related to target definition and reflects uncertainty about the presence of tumor in a voxel. Where the tumor delineation of a radiation oncology essentially gives a binary classification of each voxel, the tumor probability provides a non-binary assessment. This implies that for a perfectly calibrated model, in 100 voxels, that each have a probability of tumor presence of 50%, the histology indeed should show that 50% of those voxels contain tumor and
50% do not. **Figure 2** plots the % of voxels with proven tumor in our cohort as a function of their predicted probability of tumor presence. Ideally, a model should show the dashed line. The solid line in the figure shows that the model is well calibrated with a tumor prevalence value of 26%, which is close to the value found for the peripheral zone in the histological data of this cohort.

Although an individual delineation is a binary classification, this doesn’t mean that the radiation oncologist and radiologist have complete certainty. The variability between multiple observers is in part a reflection of this uncertainty. To evaluate the relation between observer variability and the model prediction, we therefore plotted the tumor probability as a function of the number of teams of observers that had labeled the voxel as tumor for all voxels in the peripheral zone. **Figure 3** shows that for those voxels that were labeled by all 6 teams as tumor, the model value for tumor probability indeed is high, with a median of 0.78. On the other hand, for voxels that were labeled by all 6 teams as non-tumor, the median tumor probability is 0.08. Interestingly, for voxels that were identified by an intermediate number of teams, intermediate tumor probabilities are found. The correlation between tumor probability and the number of teams identifying a voxel as a tumor is highly significant with a p-value < 0.001 and a moderately high Spearman correlation coefficient of 0.56. The concept of tumor probability is attractive for radiotherapy as it represents the certainty about tumor presence, but also correlates with the level of consensus in a group of observers. For dose differentiation between tumor and the remainder of the prostate, rather than stratification in distinct dose levels, the probabilistic interpretation of dose painting could be adopted, gradually modulating the dose based on tumor probability.

![Figure 1. Examples from 5 patients. From left to right: T2w; ADC; $K_{\text{trans}}$; H&E staining, tumor probability. The green and red contours in the tumor probability maps represent the peripheral zone region and the estimated tumor area by the model, respectively.](image-url)
Discussion and conclusion

Multi-parametric MRI is well established as a tool for staging of prostate cancer and detection of tumors inside the gland and seminal vesicles. The use of T2-weighted MRI for delineation of the prostate gland for radiotherapy results in target volumes that are about 30% smaller as compared to CT. This results in an implicit reduction of the CTV margin around the prostate, and leads to a reduction in treatment-related toxicity. However, for patients with extracapsular extension of the disease, an adequate CTV margin is required to account for subclinical disease outside the gland.

The key advantage of mp-MRI lies in the visualization of tumors inside the prostate. While the accuracy of tumor detection is high, interobserver variability in tumor delineation is sizeable. The PI-RADS system is an important step in reflecting the certainty about tumor presence in radiology reporting. An analogous system for radiotherapy tumor delineation could be helpful to indicate the certainty about parts of the delineation.

Automated methods for tumor detection may be helpful to improve the quality of tumor delineation. However, the correspondence of our tumor probability model with histology suggests that a probabilistic approach provides a more appropriate description of the pathology than a specific binary classification. The correlation between the tumor probability and number of observers identifying a voxel as tumor suggests that the model agrees with the ‘wisdom of the crowd’, and thus could serve as a reference for individual physicians in their decision making.

With mp-MRI it becomes feasible to revisit the GTV-CTV concept in radiotherapy of prostate cancer. While detection of index lesions is quite reliable, contouring variability and the low sensitivity to small lesions suggest that the remainder of the prostate should be treated as CTV. Clinical trials that investigate the options for dose differentiation, for example, with escalation to the visible tumor or dose reduction to the CTV, are therefore warranted.

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