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Review Paper

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.

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 specimen 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 cm^3 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 naive 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 K^{trans}, 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 sensitivity values 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. Schmuecking 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

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