Review Paper

Magnetic resonance imaging for prostate cancer radiotherapy

Cuong V. Dinh^a, Peter Steenbergen^a, Ghazaleh Ghobadi^a, Stijn W.T.J.P. Heijmink^b,
Floris J. Pos^a, Karin Haustermans^c, Uulke A. van der Heide^{a,*}

^a Department of Radiation Oncology, the Netherlands Cancer Institute, Amsterdam, The Netherlands

^b Department of Radiology, the Netherlands Cancer Institute, Amsterdam, The Netherlands

^c Department of Oncology, Radiation Oncology, University Hospitals Leuven, KU Leuven, Belgium

ARTICLE INFO

Article history:

Received 28 November 2015

Received in revised form 13 January 2016

Accepted 26 January 2016

Available online 5 February 2016

Keywords:

Multi-parametric MRI

Prostate cancer

Radiotherapy

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.

© 2016 Associazione Italiana di Fisica Medica. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 $< 0.1 \text{ cm}^3$ 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

* Corresponding author. Department of Radiation Oncology, the Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31205122350.

E-mail address: u.vd.heide@nki.nl (U.A. van der Heide).

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

a clear depiction of the prostatic capsule separating the CTV from the rectum and levator ani muscle, the fibromuscular stroma anteriorly and the transition from normal periopheral 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 $\pm$ 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 K^{trans} 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 (K^{trans}) using the method by Murase et al. [55] with a population-based arterial input function. Following [19], the K^{trans} map was normalized to the median value of K^{trans} in the peripheral zone, to account for measurement variability. Also, all of the parametric maps (T2w, ADC, and K^{trans}) were resampled to a grid of $2.5 \times 2.5 \times 2.5$ 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

Figure 1. Examples from 5 patients. From left to right: T2w; ADC; k^{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.

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 prob-

ability 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 2. Relation between tumor probability and pathology. For the voxels in each tumor probability interval of 0.05, the fraction of voxels identified as tumor on H&E stained slices are plotted against the center of each of the bins. The size of the circles represents the relative number of voxels in each bin. In case of an ideal model, the relation should follow the dashed line.

Figure 3. The relation between tumor probability and the number of observer teams out of a total of 6, identifying voxels as tumor in the study of [20]. The boxes identify the median and quartiles of the tumor probability for each detection rate category. The whiskers identify the limits 1.5 times the interquartile distance from the median or the outer extent of the data if this number is closer to the median. The + markers identify tumor probability values outside this range.

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.

Acknowledgements

This research was supported by the Dutch Cancer Society (NKI 2013-5937).

References

- [1] Chen ME, Johnston DA, Tang K, Babaian RJ, Troncso P. Detailed mapping of prostate carcinoma foci: biopsy strategy implications. *Cancer* 2000;89(8):1800–9.
- [2] Hollmann BG, van Triest B, Ghobadi G, Groenendaal G, de Jong J, van der Poel HG, et al. Gross tumor volume and clinical target volume in prostate cancer: how do satellites relate to the index lesion. *Radiother Oncol* 2015;115(1):96–100.
- [3] Ou Y, Shen D, Zeng J, Sun L, Moul J, Davatzikos C. Sampling the spatial patterns of cancer: optimized biopsy procedures for estimating prostate cancer volume and Gleason Score. *Med Image Anal* 2009;13(4):609–20.
- [4] Hricak H, Choyke PL, Eberhardt SC, Leibel SA, Scardino PT. Imaging prostate cancer: a multidisciplinary perspective. *Radiology* 2007;243(1):28–53.
- [5] Fuchsjäger M, Shukla-Dave A, Akin O, Barentsz J, Hricak H. Prostate cancer imaging. *Acta Radiol* 2008;49(1):107–20.
- [6] Seitz M, Shukla-Dave M, Bjartell A, Touijer K, Sciarra A, Bastian PJ, et al. Functional magnetic resonance imaging in prostate cancer. *Eur Urol* 2009;55(4):801–14.
- [7] Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;22(4):746–57.
- [8] Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Scoring systems used for the interpretation and reporting of multiparametric MRI for prostate cancer detection, localization, and characterization: could standardization lead to improved utilization of imaging within the diagnostic pathway? *J Magn Reson Imaging* 2013;37(1):48–58.
- [9] Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging – reporting and data system: 2015, version 2. *Eur Urol* 2015;S0302-2838(15)00848-9. doi: 10.1016/j.eururo.2015.08.052.
- [10] PI-RADS™. Prostate imaging – reporting and data system. <<http://www.acr.org/Quality-Safety/Resources/PIRADS->>. 2015.
- [11] Rasch C, Barillot I, Remeijer P, Touw A, van Herk M, Lebesque JV. Definition of the prostate in CT and MRI: a multi-observer study. *Int J Radiat Oncol Biol Phys* 1999;43(1):57–66.
- [12] Jonsson JH, Karlsson MG, Karlsson M, Nyholm T. Treatment planning using MRI data: an analysis of the dose calculation accuracy for different treatment regions. *Radiat Oncol* 2010;5:62.
- [13] Dowling JA, Lambert J, Parker J, Salvado O, Fripp J, Capp A, et al. An atlas-based electron density mapping method for magnetic resonance imaging (MRI)-alone treatment planning and adaptive MRI-based prostate radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;83(1):e5–11.
- [14] Bauman G, Haider M, Van der Heide UA, Ménard C. Boosting imaging defined dominant prostatic tumors: a systematic review. *Radiother Oncol* 2013;107(3):274–81.
- [15] Pickett B, Vigneault E, Kurhanewicz J, Verhey L, Roach M. Static field intensity modulation to treat a dominant intra-prostatic lesion to 90 Gy compared to seven field 3-dimensional radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;44(4):921–9.
- [16] Van Lin EN, Fütterer JJ, Heijmink SW, van der Vicht LP, Hoffmann AL, van Kollenburg P, et al. IMRT boost dose planning on dominant intraprostatic lesions: gold marker-based three-dimensional fusion of CT with dynamic contrast-enhanced and 1H spectroscopic MRI. *Int J Radiat Oncol Biol Phys* 2006;65(1):291–303.

- [17] Rylander S, Polders D, Steggerda MJ, Moonen LM, Tanderup K, Van der Heide UA. Re-distribution of brachytherapy dose using a differential dose prescription adapted to risk of local failure in low-risk prostate cancer patients. *Radiother Oncol* 2015;115(3):308–13.
- [18] Lips IM, van der Heide UA, Haustermans K, van Lin EN, Pos F, Franken SP, et al. Single blind randomized phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial. *Trials* 2011;12:255.
- [19] Groenendaal G, Borren A, Moman MR, Monnikhof E, Van Diest PJ, Philippens MEP, et al. Pathological validation of a model based on diffusion-weighted imaging and dynamic contrast-enhanced MRI for tumor delineation in the prostate peripheral zone. *Int J Radiat Oncol Biol Phys* 2012;82:e537–44.
- [20] Steenberg P, Haustermans K, Lerut E, Oyen R, De Wever L, Van den Bergh L, et al. Prostate tumor delineation using multiparametric magnetic resonance imaging: Inter-observer variability and pathology validation. *Radiother Oncol* 2015;115:186–90.
- [21] Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999;10(3):223–32.
- [22] Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging* 2007;25:145–52.
- [23] Reinsberg SA, Payne GS, Riches SF, Ashley S, Brewster JM, Morgan VA, et al. Combined use of diffusion-weighted MRI and 1H MR Spectroscopy to increase accuracy in prostate cancer detection. *AJR Am J Roentgenol* 2007;188:91–8.
- [24] Isebaert S, Van den Bergh L, Haustermans K, Joniau S, Lerut E, De Wever L, et al. Multiparametric MRI for prostate cancer localization in correlation to whole-mount histopathology. *J Magn Reson Imaging* 2013;37(6):1392–401.
- [25] Dehnad H, Nederveen AJ, van der Heide UA, van Moorselaar RJ, Hofman P, Legendijk JJ. Clinical feasibility study for the use of implanted gold seeds in the prostate as reliable positioning markers during megavoltage irradiation. *Radiother Oncol* 2003;67(3):295–302.
- [26] Schmuecking M, Boltze C, Geyer H, Salz H, Schilling B, Wendt TG, et al. Dynamic MRI and CAD vs. choline MRS: where is the detection level for a lesion characterisation in prostate cancer? *Int J Radiat Biol* 2009;85:814–24.
- [27] Langer DL, van der Kwast TH, Evans AJ, Sun L, Yaffe MJ, Trachtenberg J, et al. Intermixed normal tissue within prostate cancer: effect on MR imaging measurements of apparent diffusion coefficient and T2 – sparse versus dense cancers. *Radiology* 2008;249:900–8.
- [28] Turkbey B, Mani H, Shah V, Rastinehad AR, Bernardo M, Pohida T, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. *J Urol* 2011;186:1818–24.
- [29] Woodfield CA, Tung GA, Grand DJ, Pezzullo JA, Machan JT, Renzulli JF 2nd. Diffusion-weighted MRI of peripheral zone prostate cancer: comparison of tumor apparent diffusion coefficient with Gleason score and percentage of tumor on core biopsy. *AJR Am J Roentgenol* 2010;194:W316–22.
- [30] Nagarajan R, Margolis D, Raman S, Sheng K, King C, Reiter R, et al. Correlation of Gleason scores with diffusion-weighted imaging findings of prostate cancer. *Adv Urol* 2012;2012:374805.
- [31] Somford DM, Hambroek T, Hulsbergen-van de Kaa CA, Fütterer JJ, van Oort IM, van Basten JP, et al. Initial experience with identifying high-grade prostate cancer using diffusion-weighted MR imaging (DWI) in patients with a Gleason score $\leq 3 + 3 = 6$ upon schematic TRUS-guided biopsy: a radical prostatectomy correlated series. *Invest Radiol* 2012;47:153–8.
- [32] Doo KW, Sung DJ, Park BJ, Kim MJ, Cho SB, Oh YW, et al. Detectability of low and intermediate or high risk prostate cancer with combined T2-weighted and diffusion-weighted MRI. *Eur Radiol* 2012;22(8):1812–19.
- [33] Barrett T, Gill AB, Kataoka MY, Priest AN, Joubert I, McLean MA, et al. DCE and DW MRI in monitoring response to androgen deprivation therapy in patients with prostate cancer: a feasibility study. *Magn Reson Med* 2012;67(3):778–85.
- [34] Chang JH, Lim Joon D, Nguyen BT, Hiew CY, Esler S, Angus D. MRI scans significantly change target coverage decisions in radical radiotherapy for prostate cancer. *J Med Imaging Radiat Oncol* 2014;58(2):237–43.
- [35] Fiorino C, Reni M, Bolognesi A, Cattaneo GM, Calandrino R. Intra- and inter-observer variability in contouring prostate and seminal vesicles: implications for conformal treatment planning. *Radiother Oncol* 1998;47(3):285–92.
- [36] Milosevic M, Voruganti S, Blend R, Alasti H, Warde P, McLean M, et al. Magnetic resonance imaging (MRI) for localization of the prostatic apex: comparison to computed tomography (CT) and urethrography. *Radiother Oncol* 1998;47(3):277–84.
- [37] Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. *Semin Radiat Oncol* 2005;15(3):136–45.
- [38] Villeirs GM, Verstraete KL, De Neve WJ, De Meerleer GO. Magnetic resonance imaging anatomy of the prostate and periprostatic area: a guide for radiotherapists. *Radiother Oncol* 2005;76(1):99–106.
- [39] Sander L, Langkilde NC, Holmberg M, Carl J. MRI target delineation may reduce long-term toxicity after prostate radiotherapy. *Acta Oncol* 2014;53(6):809–14.
- [40] Bratan F, Niaf E, Melodelima C, Chesnais AL, Souchon R, Mège-Lechevallier F, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *Eur Radiol* 2013;23(7):2019–29.
- [41] Jung SI, Donati OF, Vargas HA, Goldman D, Hricak H, Akin O. Transition zone prostate cancer: incremental value of diffusion-weighted endorectal MR imaging in tumor detection and assessment of aggressiveness. *Radiology* 2013;269(2):493–503.
- [42] Rischke HC, Nestle U, Fechter T, Doll C, Volegova-Neher N, Henne K, et al. 3 Tesla multiparametric MRI for GTV-definition of Dominant Intraprostatic Lesions in patients with Prostate Cancer—an interobserver variability study. *Radiat Oncol* 2013;8:183.
- [43] Anwar M, Westphalen AC, Jung AJ, Noworolski SM, Simko JP, Kurhanewicz J, et al. Role of endorectal MR imaging and MR spectroscopic imaging in defining treatable intraprostatic tumor foci in prostate cancer: quantitative analysis of imaging contour compared to whole-mount histopathology. *Radiother Oncol* 2014;110(2):303–8.
- [44] Rouvière O, Papillard M, Girouin N, Boutier R, Rabilloud M, Riche B, et al. Is it possible to model the risk of malignancy of focal abnormalities found at prostate multiparametric MRI? *Eur Radiol* 2012;22:1149–57.
- [45] Vos PC, Hambroek T, Hulsbergen-van de Kaa CA, Fütterer JJ, Barentsz JO, Huisman HJ. Computerized analysis of prostate lesions in the peripheral zone using dynamic contrast enhanced MRI. *Med Phys* 2008;35:888–99.
- [46] Langer DL, van der Kwast TH, Evans AJ, Trachtenberg J, Wilson BC, Haider MA. Prostate cancer detection with multi-parametric MRI: logistic regression analysis of quantitative T2, diffusion-weighted imaging, and dynamic contrast-enhanced MRI. *J Magn Reson Imaging* 2009;30:327–34.
- [47] Ozer S, Langer DL, Liu X, Haider MA, van der Kwast TH, Evans AJ, et al. Supervised and unsupervised methods for prostate cancer segmentation with multispectral MRI. *Med Phys* 2010;37:1873–83.
- [48] Viswanath SE, Bloch NB, Chappelw JC, Toth R, Rofsky NM, Genega EM, et al. Central gland and peripheral zone prostate tumors have significantly different quantitative imaging signatures on 3 Tesla endorectal, in vivo T2-weighted MR imagery. *J Magn Reson Imaging* 2012;36(1):213–24.
- [49] Shah V, Turkbey B, Mani H, Pang Y, Pohida T, Merino MJ, et al. Decision support system for localizing prostate cancer based on multiparametric magnetic resonance imaging. *Med Phys* 2012;39(7):4093–103.
- [50] Vos PC, Barentsz JO, Karssemeijer N, Huisman HJ. Automatic computer-aided detection of prostate cancer based on multiparametric magnetic resonance image analysis. *Phys Med Biol* 2012;57:1527–42.
- [51] Hoeks CM, Barentsz JO, Hambroek T, Yakar D, Somford DM, Heijmink SW, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology* 2011;261(1):46–66.
- [52] Litjens GJS, Elliott R, Shih N, Feldman M, Barentsz JO, Hulsbergen-van de Kaa CA, et al. Distinguishing prostate cancer from benign confounders via a cascaded classifier on multi-parametric MRI. *Proc. SPIE 9035 Med Imaging* 2014;9035:903512. *Med Imaging* 2014: Computer-Aided Diagnosis.
- [53] Schabel MC, Parker DL. Uncertainty and bias in contrast concentration measurements using spoiled gradient echo pulse sequences. *Phys Med Biol* 2008;53(9):2345–73.
- [54] Fennessy FM, Fedorov A, Gupta SN, Schmidt EJ, Tempany CM, Mulkern RV. Practical considerations in T1 mapping of prostate for dynamic contrast enhancement pharmacokinetic analyses. *Magn Reson Imaging* 2012;30(9):1224–33.
- [55] Murase K. Efficient method for calculating kinetic parameters using T1-weighted dynamic contrast-enhanced magnetic resonance imaging. *Magn Reson Med Off J Soc Magn Reson Med Soc Magn Reson Med* 2004;51(4):858–62.