Functional MRI for tumor delineation in prostate radiation therapy

A unique property of radiation therapy is the capacity for a differential treatment, in which a high dose can be delivered to tissue with a high tumor load, whereas a lower dose is applied to treat microscopic disease around the primary tumor. This approach is termed ‘dose painting’ and is currently tested in the radiation therapy of prostate cancer. Functional MRI techniques, such as dynamic contrast-enhanced MRI and diffusion-weighted MRI, are well established for tumor localization and staging. However, application for target delineation in radiotherapy raises some specific issues: at what spatial resolution can these techniques be used reliably? What is the detection limit of the techniques? Do different techniques identify the same regions as suspicious or do they provide complimentary information? In this article we address these issues and explore how functional MRI techniques can be used for radiotherapy dose painting.

KEYWORDS: DCE-MRI diffusion-weighted MRI dose painting dynamic contrast-enhanced MRI MRI prostate radiotherapy tumor delineation

Radiation therapy is one of the primary treatment modalities for localized and locally advanced prostate cancer. In the absence of precise information about the location of cancerous tissue inside the prostate, the conventional approach has been to treat the entire gland to a more or less homogeneous dose. In several randomized trials it has been shown that escalation of the radiation dose to the prostate benefits the outcome. Up to now, several randomized trials [1–3] have showed an increase in 5-year biochemical freedom from relapse in locally advanced disease from approximately 50 to 65% when increasing the external beam radiation dose from 68 to 78 Gy. Current modern techniques, such as intensity modulated radiation therapy in combination with position verification, based on fiducial markers in the prostate, enable a safe delivery of such high doses, whilst avoiding an increase in treatment-related toxicity and a clinically relevant deterioration in quality of life [4,5].

Even further dose escalation is expected to have an additional benefit on treatment results, as evidence emerges that local recurrences are mostly found at the location of the primary tumor [6,7]. However, in particular at the dorsal side of the prostate, such a dose escalation is in conflict with the constraints required to limit rectum toxicity. For this reason, several groups have proposed limiting the boost of the radiation dose to the visible dominant lesion inside the prostate [8–11], following an approach that is termed ‘dose painting’ [12]. Here, a unique property of radiation therapy is exploited that distinguishes it from other treatment modalities.

Radiation therapy has the capacity for differential treatment, in which a high dose can be delivered to treat a dominant lesion in the prostate, whereas the remainder of the gland is irradiated with a lower dose to treat microscopic disease. This capacity sets it apart from all-or-nothing therapies, such as surgery and cryotherapy [13].

Dose painting is now being tested in clinical practice for the treatment of prostate cancer. Two studies reported on the acute toxicity of dose escalation to the dominant intraprostatic lesion of 82 Gy [14] and 95 Gy [15]. In both studies, observation of severe toxicity (CTC toxicity score [16] equal to or greater than grade 3) was minimal. Recently, a randomized Phase III trial started to investigate the benefit of a Focal Lesion Ablative Microboost (FLAME) trial, escalating the dose to the tumor from 77 Gy in the standard arm to 95 Gy in the study arm [10]. In both arms, the dose to the remainder of the prostate is kept to 77 Gy. In the FLAME trial, the tumor inside the prostate is delineated based on a combination of anatomical and functional MRI (fMRI) sequences (Figure 1 & Table 1).

The effectiveness of dose painting in the prostate relies on the high sensitivity and specificity of the imaging techniques used to visualize the tumor. T2-weighted MRI can be used for this purpose. The sensitivity and specificity of tumor detection increases when this modality is combined with dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DWI) or magnetic resonance spectroscopic imaging.
However, while the application of these imaging techniques provides great opportunities for tumor delineation in radiotherapy, it also presents some specific challenges. For a precise delineation of the tumor, images of a sufficiently high spatial resolution must be available. For functional imaging modalities, the spatial resolution at which parameter maps can be interpreted must be established. The use of multiple imaging techniques may provide complementary information, which enhances the sensitivity and specificity of the examination in a diagnostic setting. However, if suspicious volumes in multiple imaging modalities show only a partial overlap, the question arises as to what to delineate as the target volume for irradiation.

Here, we present an overview of the use of MRI in the context of target delineation for radiation therapy of the prostate. First, we address the use of MRI for delineation of the prostate. After a brief overview of the fMRI techniques used for tumor detection and staging in the

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**Table 1. Imaging and dose parameters.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GTV</th>
<th>Remainder prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ADC (mm²/s)</td>
<td>0.93*10⁻³</td>
<td>1.17*10⁻³</td>
</tr>
<tr>
<td>Mean K⁹⁰⁰⁰⁰ (min⁻¹)</td>
<td>0.85</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>94.0</td>
<td>81.4</td>
</tr>
</tbody>
</table>

*Imaging and dose parameters for the patient shown in Figure 1. ADC: Apparent diffusion coefficient; GTV: Gross target volume.*

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**Figure 1.** Dose painting in the FLAME trial based on T₂-weighted MRI (A), an apparent diffusion coefficient map, obtained from diffusion-weighted MRI (B), and a K⁹⁰⁰⁰⁰ parameter map derived from dynamic contrast-enhanced MRI (C), with dose distribution shown in (D). Imaging and dose parameters for the gross target volume and remainder of the prostate are shown in **Table 1.**
diagnostic phase, we discuss issues that are particular for their application in tumor delineation. Finally, future developments that may have an impact on radiation therapy are discussed.

**MRI for delineation of the prostate**

The impact of MRI on the delineation of the prostate gland has been well established and reviewed [17]. Comparing the intra-observer variation with CT alone and with the combination of CT and T₂-weighted MRI, many groups found that the variation decreased substantially. In particular the position of the apex could be determined more consistently. Near the apex, on CT the prostate boundary tended to be delineated 3–5 mm more caudally than on MRI, resulting in an overestimation of the prostate volume with a factor of 1.3–1.4. To improve the quality of prostate delineation on T₂-weighted MRI, McLaughlin et al. reviewed the functional anatomy as well as their visibility on T₂-weighted MRI [18]. Villeirs et al. published a guide for radiotherapists using MRI in the treatment planning for prostate cancer [19]. They review structures seen in and near the normal prostate as well as in prostates with cancer.

Rosewall et al. demonstrated that MRI also improves the quality of prostate delineation in patients with bilateral hip prostheses, where CT images suffer from artifacts [20]. In a study of seven patients, they found that the mean volume delineated by four radiation oncologists was 21% larger on CT than on MR, in line with the findings described above. The inter-observer variability also tended to be smaller, while the prostheses did not appear to cause measurable geometric distortions on the sequences used.

**MRI for detection & staging of prostate cancer**

The use of fMRI for staging of prostate cancer has been reviewed extensively [21–23]. While many studies show promising results about their diagnostic performance, a clear consensus about the use of these techniques is still lacking and the role of MRI in published guidelines is still quite limited. Nevertheless, MRI techniques are gaining recognition as an important tool for detection and localization of prostate tumors [23].

For T₂-weighted imaging alone, the staging accuracy varies considerably, with sensitivities ranging from 37 to 96% and corresponding sensitivities reported in the range between 21 and 67% [24]. The use of a 3T MRI and an endorectal coil results in an improvement of the sensitivity and specificity to 88 and 96% for experienced radiologists, while a less experienced radiologist reached values of 50 and 92%, respectively [25].

The performance of T₂-weighted MRI is improved when it is combined with DCE-MRI and MRSI [22]. DCE imaging with Gd-DTPA contrast agent reflects the properties of the vasculature, such as micro-vessel density and permeability of the vessels. The angiogenesis in tumors results in an increase in micro-vessel density, but also a highly disorganized capillary network. This is reflected in the different enhancement curves in prostate tumors and healthy tissue. A high sensitivity and specificity of tumor detection has been shown. Hara et al. uncovered 92.9% of the clinically significant cancers, with a specificity of 96.2% [26]. Kim et al. found a sensitivity and specificity of 96 and 82% for DCE-MRI, as compared with 65% and 60% for T₂-weighted MRI, respectively [27]. In the transitional zone the sensitivity of DCE-MRI was also 96%, compared with 45% for T₂-weighted MRI. However, the specificity was not significantly improved when compared with T₂-weighted MRI (51 vs 73%, p = 0.102). Using tracer-kinetics modeling with the Tofts model [28], Füterer et al. found the highest accuracy for the model parameter vₑ, representing the volume fraction of the extracellular extravascular space, with a sensitivity between 90 and 95% and a specificity between 85 and 88% [29].

Magnetic resonance spectroscopic imaging has a high specificity in the identification of tumors inside the prostate. Füterer et al. found a sensitivity between 77 and 80% and a specificity of 84–87% [29]. A high ratio of choline and creatine to citrate is indicative of cancer. However, the spatial resolution of MRSI is relatively poor, making it more difficult to detect small lesions [30–34].

Diffusion-weighted MRI has been used extensively to study the random translational motion of water molecules. In tumors, the increased cellularity restricts water motion in a reduced extracellular space, thus causing a reduction of the apparent diffusion coefficient. In the prostate, DWI has been quite successful, with sensitivities and specificities well above 80% [32–39]. Yoshimitsu et al. showed that lower apparent diffusion coefficient (ADC) values also correlate with a higher Gleason score [37].

Combining fMRI techniques in one examination further improves the performance [23,25,29]. Seitz et al. point out that MRSI, DWI and DCE-MRI all deliver additional information to...
morphologic changes depicted on $T_2$-weighted MR images [23]. They conclude that the combination of conventional MRI with fMRI techniques is more reliable for differentiating benign and malignant prostate tissue than any other diagnostic procedure.

**Application of fMRI techniques in radiation therapy**

The excellent performance of MRI techniques for tumor detection and staging creates the potential to apply these techniques for tumor delineation in radiation therapy. However, it is important to note that the diagnostic questions addressed in most studies are different from the questions that are relevant for tumor delineation. Studies reporting on the sensitivity and specificity of tumor detection mainly focus on the question if a patient has prostate cancer and only on the approximate location of that tumor. Studies regarding staging report on the accuracy of detecting capsular extension of the disease or involvement of the seminal vesicles. The answers to these questions have direct consequences for the choice of treatment. On the other hand, when patients are scheduled for radiation therapy, the presence of prostate cancer has been proven with biopsies and the stage of the disease has been established. Thus, rather than a qualitative assessment of location or capsular extension of the tumor, the precise boundaries of the lesions inside the prostate must be determined for target delineation.

**Repeatability & spatial resolution**

Delineation of a lesion within the prostate implies that for each voxel a decision has to be made as to whether it is part of the tumor or not. Therefore, it is important to know the smallest voxel size at which the parameter maps obtained from fMRI still retain meaningful information: the precision at which a parameter can be determined needs to be sufficient to distinguish values associated with tumors from values associated with healthy tissues. Image noise and day-to-day variation in a patient cause an uncertainty in these values. Both sources of uncertainty are reflected in the repeatability of a measurement, as quantified in the within-patient standard deviation.

While day-to-day variation in a patient is difficult to control, the signal-to-noise can be improved by increasing image voxels, at the cost of spatial resolution. For this reason, it is relevant to understand the relation between repeatability and voxel size: for small voxels the repeatability will be limited by image noise and may be insufficient for delineation of the tumor. For large voxels, the repeatability will mainly reflect day-to-day variations, but these voxels may be too large for delineation.

To date, results of voxel-wise repeatability in prostate cancer are lacking for fMRI techniques. The repeatability of fMRI techniques is addressed in only a few studies, mainly for the purpose of determining the detectable changes in functional parameters after treatment. In a study of 20 patients with prostate cancer, Alonzi et al. carried out two MRI examinations on subsequent days, prior to the start of treatment with androgen deprivation therapy [40]. The examination consisted of DCE-MRI as well as other fMRI techniques. The within-patient coefficient of variance (wCV) was determined for the entire prostate and regions of interest in the tumor, normal peripheral zone and transition zone. For these regions, with quite a variation in volume, wCV values were found between 13.9 and 41.9% for $K_{trans}$. From these data the threshold levels could be determined, beyond which a change in parameter could be considered a real change with a 95% confidence level. Similar numbers were reported for healthy structures and other tumors [41]. Kershaw et al. found wCV values for $K_{trans}$ in healthy prostate tissue of 31 and 27% in the peripheral zone and central gland, respectively [42]. The wCV for healthy prostate $T_2$ values was 3%.

A key problem in the acquisition and analysis of DCE-MRI data is the accurate measurement of the arterial input function (AIF), needed for absolute quantification. Owing to the non-linear relationship between the signal and contrast agent concentration and artifacts, such as $T_2$*- effects, B1-field inhomogeneities and in-flow effects, the repeatability of AIF measurements tends to be poor with correlation of variance values of up to 50% in peak height and 25% in the tail of the AIF [43]. The impact of these variations is mostly a scaling of the tracer kinetics parameter map $K_{trans}$. It is clear that these difficulties have an impact on the repeatability of the DCE-MRI examination. Furthermore, it explains why between studies of different institutes large differences are found in the parameter range of $K_{trans}$ in healthy (0.06–0.60 min$^{-1}$) and cancerous (0.18–1.26 min$^{-1}$) prostate tissue (Table 2) [44–50].

The challenges described above can be circumvented with DCE-CT, which has become feasible with multislice CT scanners that allow imaging of sufficiently large slabs at once [51]. Jeukens et al. investigated the impact of image
noise on the confidence intervals of tracer kinetics model parameters [52]. By integrating the signal in a volume of approximately 0.1 cc, noise levels could be obtained that allow for reliable tracer kinetics modeling. Korporaal et al. studied the repeatability of DCE-CT as a function of voxel size [53]. A group of 29 patients underwent two DCE-CT examinations within 1 week prior to radiation therapy. Parameter maps of $K^{\text{trans}}$ and other parameters in the Tofts model were calculated at 15 different image resolutions. For the group of patients, the median $K^{\text{trans}}$ in the suspected tumors was 0.24 min$^{-1}$ and in the regions of interest in the healthy peripheral zone it was 0.11 min$^{-1}$. In a voxel-wise comparison between the two examinations, the within-voxel standard deviation was determined. The day-to-day variation of the DCE-CT examination was reflected in a wSD for $K^{\text{trans}}$ of 0.027 min$^{-1}$, obtained from signals integrated in a voxel of 2.6 cc. For signals integrated in a volume of 0.15 cc, corresponding to a cube of 5.3 mm$^3$, a wSD of 0.047 was found. Thus, at this voxel size, the uncertainty in $K^{\text{trans}}$ is sufficiently small to allow discrimination between values associated with tumor and healthy tissue. The precise implication of these results for MRI needs to be investigated. However, as the signal-to-noise ratio in MRI should be higher than in CT, a spatial resolution similar to that found in DCE-CT should be feasible.

For diffusion-weighted imaging, the repeatability of examinations of the prostate was studied by Gibbs et al. in eight healthy volunteers [54]. The repeatability of the ADC values varied between 10 and 35%, depending on experimental conditions. The authors also showed the impact of signal-to-noise on the repeatability by varying the number of signal averages. Increasing the number of signal averages from 1 to 16, the repeatability improved from 10 to 4%. Varying the size of the region of interest from 0.3 to 1.7 cc seemed to have little impact on the repeatability.

Differences in methodology between institutions and quantification problems inherent to the acquisition limit the quantification of functional parameters. For DWI-MRI, researchers have proposed a consensus approach to address this issue [55]. For DCE-MRI the situation is not as clear. Although, in particular the Tofts model has contributed to the agreement about nomenclature and definitions in tracer kinetic modeling [28], there is still insufficient consensus about the standardization of DCE-MRI imaging protocols.

### Use of an endorectal coil

The application of fMRI techniques for tumor delineation in the prostate poses specific challenges. The scan protocols that have been found to be optimal for prostate scanning typically involve the use of an endorectal coil owing to its superior signal-to-noise. In particular at 1.5T, the use of an endorectal coil, combined with a pelvic phased-array coil is recommended for diagnostic imaging [21]. At 3T the improved signal-to-noise ratio of the high-field-strength systems can compensate some of the signal loss when scanning with only a phased-array coil. Figure 1 & Table 1 show a good signal-to-noise for the $T_2$-weighted image scanned at 3T with a phase-array coil, yielding an in-plane resolution of 0.78 mm and a slice thickness of 3 mm. In addition, proton MR spectroscopy was shown to be feasible without an endorectal coil [56]. Nevertheless, Heijmink et al. demonstrated that the image quality of $T_2$-weighted images of the prostate improved significantly at 3T with the use of an endorectal coil when compared with a body array coil [57].

For radiotherapy, the deformation of the prostate by the endorectal coil is problematic, as it results in an image of the prostate that is not representative of the situation during the radiation therapy. Heijmink et al. studied the change in prostate shape by comparing 3T MRI images made with and without an endorectal coil [58]. They found an average decrease of the antero-posterior diameter of 5.5 mm after insertion of the endorectal coil. The mean right-to-left and cranio-caudal diameter increased by 3.5 and 2.2 mm, respectively. The mean volume of the prostate also decreased significantly by 17.9% for the total prostate, 21.6% for the peripheral zone and 14.2% for the central gland. These results are consistent with those found by Kim et al., also demonstrating that an expandable coil caused more deformations than a rigid coil [59].

### Table 2. Overview of dynamic contrast-enhanced MRI $K^{\text{trans}}$ values (min$^{-1}$) for tumor and healthy peripheral zone in the literature, demonstrating the wide spread of values between institutes.

<table>
<thead>
<tr>
<th>Healthy peripheral zone</th>
<th>Prostate cancer</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 ± 0.08</td>
<td>0.28 ± 0.13</td>
<td>[44]</td>
</tr>
<tr>
<td>0.34 ± 0.17</td>
<td>0.59 ± 0.31</td>
<td>[30]</td>
</tr>
<tr>
<td>0.60 ± 0.56</td>
<td>1.26 ± 0.54</td>
<td>[45]</td>
</tr>
<tr>
<td>0.23 ± 0.25</td>
<td>0.47 ± 0.57</td>
<td>[46]</td>
</tr>
<tr>
<td>0.13</td>
<td>0.27</td>
<td>[47]</td>
</tr>
<tr>
<td>0.50, range 0.20–0.82</td>
<td>1.09, range 0.46–1.97</td>
<td>[48]</td>
</tr>
<tr>
<td>0.06 ± 0.03</td>
<td>0.18 ± 0.06</td>
<td>[49]</td>
</tr>
<tr>
<td>0.29, range 0.09–0.87</td>
<td>0.36, range 0.16–1.28</td>
<td>[50]</td>
</tr>
</tbody>
</table>
In a rather rigorous approach to deal with this problem, Van Lin et al. proposed to use a rectal balloon while making the planning CT scan and during all 35 radiation therapy treatment fractions [10]. While additional benefits of a rectal balloon are claimed, in particular for minimizing the radiation exposure of the rectal wall [60], the patient discomfort, as well as workload of this procedure, seems to prevent widespread use. An alternative is the use of nonrigid registration techniques to correlate MRI images made using an endorectal coil with planning CT images made without it. Alternatively, the use of a colorectal coil, rather than an endorectal coil, could be investigated in the hope that it would not cause large distortions of the prostate while yielding a high signal-to-noise. However, in practice, the endorectal coil is not commonly used in MRI examinations intended for radiation therapy treatment planning. Consequently, the signal-to-noise of the fMRI is not as good, leading to a reduced spatial resolution and sensitivity for detecting small lesions.

**Detection limit**

Prostate cancer is a heterogeneous disease that is often found with multiple tumor foci in the prostate. Chen et al. determined the volume and location of tumor foci in 180 prostatectomy specimens and found that 83% of the prostates had more than one tumor focus, with a median of three foci [61]. The volume of the tumors varied from 0.01 to 19.06 cc, with a median of 1.39 cc. Similar results were found recently by Bott et al. [62]. They showed that the median volume of the largest (index) tumor was 0.95 cc (range: 0.1–18.2 cc), whereas the median volume of the largest secondary tumor was 0.2 cc (range: 0.05–1.7 cc).

Schmackeck et al. investigated the detection level for lesion characterization in the prostate using DCE-MRI and MRSI [63]. In this study they used the commercially available MR sequences on a 1.5T scanner. While this study confirms the high sensitivity and specificity of DCE-MRI (82 and 89%, respectively) and somewhat lower values for MRSI (sensitivity: 68%; specificity: 67%), the study also demonstrated that prostatic intraepithelial neoplasia lesions are not detected by either technique. For DCE-MRI, lesions smaller than 3 mm and/or containing less than 30% cancer cells could not be detected. For MRSI the cut-off level was 4 mm and/or less than 40% tumor cell content. Consequently, in cases with diffuse tumor growth they found that the tumor volume tended to be underestimated when using these techniques.

A similar conclusion was drawn for DWI-MRI by Langer et al. in a study comparing tumors in histology with diffusion-weighted imaging and quantitative T2-mapping [64]. Tumors in which more than 50% of their cross-sectional areas contained primarily normal peripheral zone tissue were designated as ‘sparse’ tumors. These tumors were found to have similar ADC and T2 values to normal peripheral zone tissue, whereas in ‘dense’ tumors a lower ADC and T2 were found. This implies that prostate tumors may hold regions that are intrinsically invisible with these imaging techniques, thereby limiting the accuracy of target delineation.

Within radiation therapy, the gross target volume (GTV) is used to identify the tumor that is visible to the radiation oncologist. The clinical target volume (CTV) is the volume containing ‘subclinical’ disease, for example a low density of tumor cells, below the detection threshold of the imaging techniques available. For application of fMRI techniques in radiotherapy, information about the detectability of small lesions and tumor volumes holding a low fraction of cancerous cells provides us with clues about the distinction between GTV and CTV. Typically, the dose required for control of the tumor depends on the density of tumor cells. Thus, information about the detection threshold is critical for improving our understanding of the dose requirements of visible tumors and the rest of the prostate.

**Making delineation decisions based on a combination of MRI techniques**

As described above, an MRI examination for staging prostate cancer preferably involves a combination of techniques. Where individual techniques may suffer from either a lower sensitivity (e.g., MRSI) or specificity (e.g., DCE-MRI), their combination results in a high accuracy for detecting and staging prostate cancer.

While combining different techniques is advantageous in a diagnostic setting, a problem emerges for tumor delineation: if different techniques show conflicting results about the presence of tumor, it is unclear which voxels should be included in the target volume. Even if multiple techniques indicate the presence of a tumor in a particular region of the prostate, the boundaries of this tumor may not be the same in all modalities.

Groenendaal et al. investigated if DCE-MRI and DWI provide consistent information on a voxel level [48]. Owing to uncertainty regarding
sue properties that are detected in each of the imaging modalities is whole-mount section histology for therapeutic radiology and oncology (GEC-ESTRO) [65], the GTV can be defined as the volume that is consistently identified as tumor on all imaging modalities. A high-risk CTV can be defined, which involves the voxels that are suspected based on any of the imaging modalities, but not consistently identified on all. The CTV can then be regarded as the volume of subclinical disease, not identified as suspicious by any of the imaging modalities [48,66]. In a focal boost treatment plan, the high-risk CTV essentially functions as a margin around the GTV, in which dose escalation is allowed, but not required (Figure 2).

Pathological validation

The gold standard for validation of imaging modalities is whole-mount section histology of prostatectomy specimen. To appreciate the impact of tumor heterogeneity on the images, a better understanding is required of the tissue properties that are detected in each of the imaging techniques. This calls for pathology studies of prostate cancer that do not primarily focus on the tumor location, but rather on properties such as cell density (‘cellularity’) and microvessel density. Particularly interesting are the regions that yield conflicting information from different imaging modalities. However, accurate validation of these techniques with a high spatial accuracy is very challenging. Processing and registration of the prostatectomy specimen needs to be very precise. Since the exact tumor location and extent are not as critical in a diagnostic setting, the validation of MR techniques has mainly been carried out on larger parts of the prostate, such as octants [29,30,45].

In particular, when an endorectal coil is used during imaging, the deformations of the prostate between images and histology slices can be large. Shah et al. proposed to improve the spatial correlation by placing the prostate specimen in a mold that was fabricated to match the in vivo shape of the prostate [67]. Specific care was taken to cut the tissue blocks in the same direction as the imaging slices.

Turkbey et al. applied two methods to correlate MR images to whole-mount section pathologic sections [68]. In the stringent approach, a one-to-one correlation was determined between imaging and pathologic findings. In an alternative approach, neighboring regions on the 3D grid were also included in the correlation, assuming that any displacement of a tumor focus due to distortions of the pathologic sections would be limited in distance. As expected, a significant increase in sensitivity and specificity was found when including the neighboring regions in the analysis.

Park et al. proposed a method to improve the spatial correlation between images and histology slices by breaking up the registration procedure in subregistration steps involving intermediate modalities [69]. To this end, each histology section is registered to a block face photograph of the prostate. A stack of block-face photographs, constituting an image of the prostate, is registered to an ex vivo MR image of the prostate taken after the prostatectomy. This image is finally registered onto the in vivo MRI of the prostate. Following this method, they found registration errors between histology and in vivo MRI data of 3.7 and 2.3 mm in two patients. Following a similar approach for five patients, Groenendaal et al. also found registration errors of 2–3 mm [70]. A comparison of delineations of tumors on MRI with pathology, showed that 85–100% of the tumor...
was included in the delineated volume when a registration uncertainty of 3–5 mm was taken into account.

Future perspective

Methods for automatic segmentation based on multimodality MRI

The combination of conventional MRI with fMRI techniques is quite successful in differentiating benign and malignant prostate tissue. As a result, the use of fMRI techniques combined with T2-weighted imaging is gaining recognition for staging of prostate cancer. For tumor delineation, some uncertainties still exist, in particular regarding cut-off levels for functional parameter maps and regarding the spatial resolution of these techniques.

To increase the robustness of the use of multiple imaging techniques, several groups have proposed an automated analysis of the images. Vos et al. use a support vector machine as a

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Figure 2. Pathology and imaging data of a patient with a tumor in the right lateral side of the peripheral zone. For the ADC a threshold of $1.1 \times 10^{-3}$ mm$^2$/s was used, for Ktrans a threshold of $0.18$ min$^{-1}$. The bottom image shows in white the voxels where both modalities overlap, in gray the voxels where the modalities provide conflicting information. Black voxels are not suspicious of the presence of tumor.

ADC: Apparent diffusion coefficient.
classifier that is used as a measure of likelihood of malignancy [71]. The diagnostic accuracy (AUC) obtained for differentiating prostate cancer from nonmalignant disorders in the peripheral zone was 0.83. However, in radiotherapy, the challenge is the delineation of the tumor, rather than the diagnosis. Thus, for each voxel the radiation oncologist needs to decide if it is part of the tumor or not. In a voxelwise analysis of $T_2$-weighted MRI, DWI and DCE-MRI, Langet et al. used logistic regression to create an objective model for mapping tumors in the peripheral zone [72]. Ozer et al. took this work one step further and studied a variety of supervised and unsupervised learning methods to derive a segmentation of prostate tumors [73]. Their results show that supervised methods, such as support vector machines, perform better than unsupervised methods, particularly when a combination of MRI modalities is used. Nevertheless, the outcome of such tumor prediction models will have some remaining uncertainty, because of limitations in sensitivity and specificity [73] of the model as well as in repeatability of the MRI examinations. For application in radiotherapy, this remaining uncertainty must be incorporated in the target definition. As discussed above, this could again be carried out by explicitly identifying distinct risk levels [66]: voxels with a high risk of containing tumor could be identified as GTV. Voxels with a low risk of containing macroscopic tumor may hold microscopic disease and could be identified as CTV. For voxels with an intermediate risk, a high-risk CTV was proposed. When boosting the dose to the GTV, the high-risk CTV functions as a margin around the GTV, where a higher dose is allowed.

Testing the effectiveness of dose painting in the prostate

The evaluation of the effectiveness of dose painting in prostate cancer needs to be established in randomized clinical trials. To date, one Phase III trial has started [101]. Although such randomized trials are necessary, the ‘classical’ end points are not very strong for evaluating the effectiveness of the dose painting itself. In the experimental arm, the patients receive a higher dose than in the standard arm. Thus, even if the dose escalation is erroneously given in a location without tumor load, the tumor control in the experimental arm cannot be lower than in the standard arm. Similarly, the treatment-related toxicity cannot be lower.

To deal with this problem, it is important to investigate the precise location of a recurrence. In particular if a recurrence is local, it is important to establish what the dose level was at that precise location. Van Vulpen et al. showed the feasibility of this approach in a study of 14 patients, treated with external-beam radiotherapy and brachytherapy [74].

Several MRI techniques have been proposed to image local recurrences in prostate cancer, as reviewed by De Visschere et al. [75]. Follow-up imaging after radiotherapy needs to take into account the fact that many changes occur in the prostate, that are not related to outcome, such as inflammation, glandular atrophy, fibrosis and prostate shrinkage [75]. In particular, MRSI shows a clear benefit for prostate cancer follow-up after treatment [76,77]. In a few studies on DCE-MRI in localizing local recurrences, a superiority of DCE-MRI over $T_2$-weighted MRI was shown. In patients with a history of radiotherapy contrast, DCE imaging offers a favorable contrast between the early enhancing recurrence and the slowly enhancing postradiation fibrosis [78,79].

Imaging tumor aggressiveness & radiosensitivity

For guiding the clinical choices regarding dose to the tumor for individual patients, it is important to identify which tumors require a high dose and for which tumors the current dose of approximately 78 Gy would suffice. Properties such as cell density and microvessel density are likely to have an impact on tumor radiosensitivity. Several studies present evidence of the correlation of choline-containing compounds in prostate tumors and their aggressiveness [80,81]. Biopsy studies also revealed altered levels of polyamine metabolites, suggesting a negative correlation between polyamines and Gleason score [80]. A qualitative assessment of polyamines has been performed in vivo by MRSI at 1.5T [82]. Evidence is also emerging that ADC values reflect Gleason score. Tamada et al. found a significant negative, although not very strong correlation, between ADC in the peripheral zone and the Gleason score (rho = -0.497; p = 0.001) [83]. Similar results were also found by Yoshimitsu et al. [84].

Hypoxia is another important factor in determining the radiosensitivity of a tumor. While DCE-MRI reflects the properties of the vasculature, blood oxygen-level dependent MRI has been tested in prostate to characterize the oxygenation in the tumor more
directly. Hoskin et al. used multiple gradient-recalled echo images at varying echo times to calculate an $R_2^*$ map [85]. In combination with estimates of the blood volume from dynamic susceptibility contrast MRI, this was used to assess the oxygenation of prostate tissue. Nevertheless, the interpretation of these data remains difficult.

Chopra et al. also showed a correlation between $R_2^*$ and hypoxia measurements using a polarographic needle electrode [86]. However, they also found a strong correlation between $R_2^*$ and $T_2$, concluding that further development is required to extract oxygenation effects robustly from tissue signal relaxation metrics.

When the value of these functional imaging modalities is established for characterizing tumor aggressiveness and radiosensitivity, they can be expected to play an important role in selection of the most appropriate dose range, optimizing the balance between the risk of toxicity and the likelihood of achieving tumor control.

### Conclusion

The value of fMRI techniques for detecting prostate cancer is now well established within the radiology community. The potential of these techniques is also beginning to receive recognition within the radiation therapy community, as indicated by the various planning studies on focal boosting of prostate tumors. Nevertheless, their application in clinical practice is still limited to a few institutes, mainly within research hospitals. Tumor delineation is currently a manual procedure, where a radiation oncologist and radiologist decide what to include in the target based on the available images and clinical information.

For a more widespread application, it seems that the robustness of the techniques must be improved. As prostate cancer is a multifocal disease, the optimal spatial resolution needs to be established at which fMRI techniques can be used for tumor delineation. Repeatability studies that study the variation of imaging parameter maps at a voxel level are required. As data from

### Executive summary

**Functional MRI techniques for tumor delineation in radiation therapy**
- The potential of functional MRI techniques for tumor delineation has begun to receive recognition within the radiation therapy community, as indicated by the various planning studies on focal boosting of prostate tumors.
- The toxicity and effectiveness of dose painting in prostate radiation therapy is being tested in clinical trials.
- When patients are scheduled for radiation therapy, the presence of prostate cancer has been proven with biopsies and the stage of the disease has been established. Thus, rather than a qualitative assessment of location or capsular extension of the tumor, the precise boundaries of the lesions inside the prostate must be determined for target delineation.
- Tumor delineation essentially means that for each voxel a decision has to be made if it is part of the target volume or not.

**Detection limits**
- Several studies have determined detection limits for dynamic contrast-enhanced MRI and diffusion-weighted MRI. Detectability depends not only on size, but also the percentage of cancerous cells within a volume.
- In radiation therapy, sparse tumors may require a lower dose than dense tumors.

**Repeatability & spatial resolution**
- For tumor delineation we need to know what voxel sizes can be used meaningfully for making delineation decisions. Therefore, the repeatability of functional MRI examinations must be established as a function of voxel size.
- For dynamic contrast-enhanced CT, voxels of 0.15 cc showed a within-standard deviation of $K_{trans}$ of 0.047 min$^{-1}$, which is sufficient to discriminate tumor from healthy tissue. At least a similar spatial resolution should be feasible for MRI.

**Delineation decisions based on a combination of MRI techniques**
- Owing to tumor heterogeneity, different MRI techniques may show conflicting results about the presence of tumor in a voxel. In these cases it is unclear which voxels to include in the target volume.
- A pragmatic approach to deal with this uncertainty is to classify multiple target volumes according to risk. In a focal boost treatment plan, the intermediate risk target volume essentially forms a margin around the high-risk tumor volume.
- Owing to tumor heterogeneity, validation of (combinations of) imaging modalities must be carried out at a high spatial resolution. However, as the registration accuracy between histology and imaging data sets is currently limited to 2–3 mm, the validation of even smaller features in images is not feasible.

**Future perspective**
- For a more widespread application of functional MRI techniques for delineation of prostate tumors, the robustness of these techniques must be improved. Automated analysis of imaging, using support vector machines or logistic regression models may be helpful for this purpose.
- To test the effectiveness of dose painting in clinical trials, it is important to correlate the precise location of a recurrence with the original location of the tumor as well as the given radiation dose. Therefore, diagnostic techniques for locally recurrent prostate cancer are essential.
multiple MRI techniques reflect tumor heterogeneity, validation of this heterogeneity with pathology is required to identify which parts of the suspected volumes should be included in the target volume for boosting the radiation dose. Relatively simple methods to deal with this heterogeneity, such as the use of target volumes for different risk levels, need to be improved by using automated methods to translate multiparametric data into appropriate segmentations.

In conclusion, fMRI techniques for delineating prostate cancer are now being used in radiation therapy dose painting. At least one randomized Phase III trial is currently under way to investigate the benefit of a focal boost to the visible tumor inside the prostate \[10\]. Nevertheless, to expand the use of fMRI techniques beyond a limited number of research centers, their robustness needs to be improved.

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Papers of special note have been highlighted as:


**Compact introduction to the potential of dose painting in radiation therapy in comparison to other treatment modalities, and the role of imaging.**

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** Discusses the capacity of diffusion-weighted MRI to detect tumors with different percentages of cancerous cells.


** Website

ClinicalTrials.gov: FLAME: investigate the benefit of a focal lesion ablative microbost in prostate cancer
www.ClinicalTrials.gov