ORIGINAL ARTICLE

Accurate prostate tumour detection with multiparametric magnetic resonance imaging: Dependence on histological properties

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Abstract

Background. To benefit most of focal treatment of prostate tumours, detection with high precision of all tumour voxels is needed. Although diffusion-weighted imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) have good diagnostic performance, perfect tumour detection is challenging. In this study, we investigated the variation in prostate tissue characteristics Gleason score (GS), cell density (CD) and microvessel density (MVD) to explain the limitations in tumour voxel detection with a MRI-based logistic regression model. Material and methods. Twelve radical prostatectomy patients underwent a pre-operative 3.0T DWI and DCE-MRI exam. The MRI scans were used to calculate voxel-wise tumour probability with a logistic regression model for the peripheral zone (PZ) of the prostate. Tumour probability maps were correlated and validated with whole-mount histology. Additionally, from the whole-mount histological sections CD, MVD and GS were retrieved for every single voxel. GS, CD and MVD of true- and false-positive voxels and of true- and false-negative voxels were compared using Mann-Whitney U-tests. Results. False-negative tumour voxels had significantly lower CD and MVD (p < 0.0001) and were similar to non-tumour PZ. True-positive detected tumour voxels had high CDs and MVDs (p < 0.0001). In addition, tumour voxels with higher GS showed a trend towards more frequent detection (p = 0.06). Tumour voxels with GS ≥ 3 + 4 showed higher CD and MVD compared to tumour voxels with GS 3 + 3 (p < 0.0001). Conclusion. Tumour voxels with low CD and MVD resemble healthy tissue and are limiting tumour voxel detection using DWI and DCE-MRI. Nevertheless, the most aggressive tumour voxels, containing high CD, MVD and GS, are more likely to be detected and can therefore be treated with high dose using focal therapy or focal boosting.

Evidence is emerging that local recurrences of prostate tumours after radiotherapy are often seen at the original tumour site [1]. Therefore, an additional radiation boost dose to this tumour could improve the tumour control probability. By limiting the boost to the visible tumour, radiation toxicity to the organs at risk such as rectum and bladder may be minimised [2,3]. Treatment side effects can be reduced with targeted focal therapy to the index lesion only without treating the whole prostate gland [4]. In this case it is essential that all significant cancer is detected to allow for proper selection of patients for focal therapy. Treatment strategies like focal boosting and focal therapy therefore require precise delineation of the entire tumour area.

Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) have a high sensitivity and specificity for tumour detection [5,6]. However, the use of multiparametric MRI in radiotherapy clinic requires improved tumour detection accuracy. First, on voxel level, DCE-MRI and DWI appear to provide complementary information about the presence of tumour, which, however, does not always point exactly at the same tumour locations. Second, the performance of simple thresholding of MRI parameters such as Ktrans and maps of apparent diffusion coefficients (ADCs) is insufficient for accurate delineation of all tumour voxels [7].
To deal with these challenges, in a previous study, we created a logistic regression model based on DWI and DCE-MRI [8]. This model had a high diagnostic performance (AUC = 0.89). However, certain tumour parts remained undetected and parts of the non-tumour peripheral zone (PZ) were incorrectly assigned as tumour tissue. The explanation for these limitations may be found in the tissue’s cell density and microvessel density, as the MR techniques DWI and DCE-MRI are believed to reflect these tissue properties [9–11]. Both non-tumour PZ tissue and prostate tumour tissue can be highly heterogeneous with regard to these characteristics, affecting tumour detectability [12].

In this study, the limitations in sensitivity and specificity of tumour voxel detection with a logistic regression model are explored in relation to the cell density (CD) and microvessel density (MVD) of malignant and benign PZ tissue of the prostate. Furthermore, the limitations in sensitivity are related to the GS.

**Material and methods**

**Patients**

This study was approved by the institutional review board and informed consent was obtained from all patients. Twelve patients were included in this study. All patients had biopsy proven prostate cancer and were scheduled for a Robotic Assisted Laparoscopic Prostatectomy (RALP). Clinical characteristics are shown in Table I.

**Imaging**

Prior to prostatectomy all patients underwent a T2w, balanced TFE, DWI and DCE-MRI exam using a 3T Philips Achieva MR scanner (Philips, Best, The Netherlands). To prevent prostate deformations, no endorectal coil was used. Before the MR exam, a urinary catheter was inserted to visualise the urethra in order to facilitate registration of MR-images and histological slices. MRI acquisition details are listed in Supplementary Appendix 1 (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2013.837581).

**Logistic regression model**

In a previous study, a logistic regression model was developed, which can be used for predicting the presence of tumour tissue. Experienced observers delineated highly tumour suspicious regions and healthy regions on MRI scans of radiotherapy patients. Tumour suspiciousness was based on hypointense values on T2w scans, low ADC and high K\textsubscript{trans} values. The voxels in these regions were used to create the model. The final model consisted of: the ADC and K\textsubscript{trans} value in a voxel, the minimum and maximum of the ADC and K\textsubscript{trans} in a kernel around this voxel and the relative y (ventral-dorsal direction) and z (caudal-cranial direction) coordinate. The model was validated on a group of prostatectomy patients and yielded high diagnostic performance (mean AUC = 0.89). The continuous model outcome, ranging from 0 to 1, was stratified based upon the positive- and negative-predictive values. A threshold of 0.72 was used, which resulted in a sensitivity of 0.89 and a specificity of 0.72 for voxel-wise tumour detection [8].

**Histopathology**

After prostatectomy, the left and right prostate surfaces were inked with different colours. The whole prostate was fixed in formaldehyde for approximately two days. Three carbon rods were inserted in the prostate specimen to facilitate the registration process after slicing of the prostate. Subsequently, we cut the prostate into slices of 3 mm. The precise thickness of these macroscopic slices was verified with a digital vernier caliper. Finally, whole-mount microscopic sections of 4 \( \mu \)m were cut from the macroscopic paraffin embedded slices and stained with haematoxylin-eosin (H&E). A pathologist delineated the tumour areas on the H&E sections. Each tumour region was assigned with a GS in consensus by two observers. Digital photographs were taken of the macroscopic slices and the H&E sections including delineations were digitised using a flatbed scanner (Epson Expression 10000XL).

**Registration between histopathology and MR images**

To compare the MR data with histopathology, the MR images were registered to the H&E sections, as described previously by Groenendaal et al. [13]. Three steps were performed: 1) registration of the H&E sections to the macroscopic slices; 2) 3D
reconstruction of the prostate specimen from the macroscopic slices; and 3) registration between the prostate reconstruction and the T2w MR images. On average the registration error of this method was 2–3 mm [13]. For the last eight patients, the protocol was improved by embedding the prostate in agarose gel (5%) prior to slicing, to match for the sectioning plane of the prostate and the MRI plane. This improvement decreased the registration error with approximately 0.5 mm. For all patients, the registration error between the MR images and histopathology was on average about 1 voxel (reconstructed voxel size 2.5 × 2.5 × 2.5 mm³) [13].

**Immunohistochemical vessel staining**

Tissue sections were deparaffinised, endogenous peroxidase activity was blocked and antigen retrieval was performed. Sections were incubated with an anti-CD31 monoclonal antibody (mouse-anti-human CD31, Novocastra). Subsequently, sections were incubated with HRP-conjugated secondary antibody (Novolink Polymer Detection System, Leica Microsystems) and diaminobenzidin and counterstained with haematoxylin. Throughout, appropriate positive and negative controls were used.

**Tissue evaluation**

Three microscopic slices per patient, containing the dominant tumour nodule and normal PZ, were chosen for further analysis and digital whole-slide images at microscopic resolution were created. Analysis of CD and MVD was performed in a grid of 2.5 × 2.5 mm², corresponding to the MRI voxels. The H&E stained sections were used for the determination of the CD. With the IHC Nuclear Algorithm v8 in ImageScope v10.0 (Aperio Technologies, Vista, CA, USA) the absolute number of cell nuclei per voxel was identified. Minimum detectable nuclear size was set at 20 μm². The Microvessel Analysis Algorithm v1 was used to identify CD31-stained blood vessels. The minimum vessel area threshold was set at 50 μm² to ignore aspecific background staining. To compensate for variation in staining intensity, the settings of the algorithms were evaluated qualitatively and optimised for every batch by adjusting them on test regions.

**Data analysis**

The registration error of about one voxel (2.5 × 2.5 × 2.5 mm³) results in a misalignment between the suspicious region on the MR images and the tumour on the H&E stained sections. This may result in incorrect classification of voxels as either false negative or false positive. To exclude false-positive voxels from the data, non-tumour voxels were only taken into account if all the neighbouring voxels contained non-tumour PZ tissue only. This correction method, however, results in a large reduction in the number of eligible voxels. For tumour, the amount of remaining voxels was considered too small for analysis. For tumour voxels we therefore chose an alternative approach to compensate for the registration error: we considered a tumour voxel as correctly detected when at least one neighbouring voxel contained tumour tissue. This approach was previously used by Turkbey et al. [14] on a regional level.

CD and MVD were compared for the true-positive, false-negative, false-positive and true-negative voxels. For these analyses a Mann-Whitney U-test was used (SPSS version 16.0, SPSS, Chicago, IL, USA). We used a Kruskal-Wallis test to determine if MR tumour detectability was related to GS. Furthermore, we tested if CDs and MVDs differed for GS = 3 + 3 and GS ≥ 3 + 4, using a Mann-Whitney U-test. The Bonferroni method was used to correct for multiple testing, p-values < 0.05/5 = 0.01 were considered significant.

**Results**

The detailed and heterogeneous data in this study is illustrated in two figures. In Figure 1, the histopathological properties of one prostate slice are depicted. The figure shows that prostate (tumour) tissue can be highly heterogeneous, both on the CD and MVD level. Especially on MVD, both PZ tumours are very different (Figure 1g). The heterogeneity in tissue characteristics is partly reflected by differences in Gleason patterns within a single tumour (Figure 1b). Given the relatively large voxel sizes on MRI, MR voxels are likely to show a mixture of different CD, MVD and Gleason patterns.

Figure 2 shows an example of the relation between the MR images and the spatial distribution of CD and MVD. In this figure an ADC map (a) and K¹rans map (b) are shown, as well as the prediction of the logistic regression model (c). On these images two tumours are delineated. The left tumour has on average a low ADC (0.93 × 10⁻³ mm²/s) and a high normalised K¹rans (3.2). The right tumour consists of high ADC values (mean 1.2 × 10⁻³ mm²/s) and low K¹rans values (mean 1.1), associated with healthy tissue. Due to its low ADC and high K¹rans, the left tumour was detected and even overestimated by the logistic regression model (Figure 2c). In contrast, a large part of the right tumour was not detected by the logistic regression model. The two tumours also differed on CD and MVD (Figure 2e and f). The left tumour consists of voxels with a high
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CD and MVD and has a GS of 3 + 4 (mean CD: 5437 cells/mm², mean MVD: 241 vessels/mm²), whereas the CD and MVD in the right tumour are low with GS 3 + 3 (mean CD: 2657 cells/mm², mean MVD: 99 vessels/mm²).

Similar results were found in all patients. The MR detected tumour voxels (true positives) had on average the highest CD, followed by the MR non-detected tumour voxels (false negatives) (median CD true positive: 3560 cells/mm², MR false negative: 2910 cells/mm², median MVD true positive: 115 vessels/mm², false negative: 90 vessels/mm²) (Figure 3a and b). These values were compared with CDs and MVDs in non-tumour PZ voxels that were either incorrectly assigned by the model as tumour voxel (false positives) or correctly as non-tumour (true negatives). CDs and MVDs in the false-positives and true-negatives groups were 3015 cells/mm², 95
vessels/mm² and 2480 cells/mm², 85 vessels/mm², respectively. These differences in CD and MVD were all significant (p < 0.0001), except for the differences between the false-negative and false-positive voxels (CD: p = 0.198, MVD: p = 0.234). Also, false-negative tumour tissue had similar MVD as the MVD found in the non-tumour PZ (p = 0.233).

In Figure 4, the percentages of true-positive and false-negative tumour voxels are plotted for the different GSs. We found a trend that the tumour voxels with higher GS were easier to detect (p = 0.06). This is in line with the finding that tumour tissue with a GS ≥ 3 + 4 showed a higher CD and MVD compared to tumour tissue with a GS of 3 + 3 (p < 0.0001).

**Discussion**

Precise prostate tumour detection, and therefore tumour delineation, is complicated by the large spread in ADC and K\textsuperscript{trans} values inside the tumour. In a previous study, we presented a logistic regression model with a high diagnostic performance (AUC = 0.89) for detection of tumour voxels in the prostate PZ [8]. The output of this model can be used for tumour delineation. However, parts of tumours were non-detected by the model. Similarly, parts of non-tumour PZ tissue were incorrectly assigned as tumour tissue. As the model was generated based on clinical data, it can be inferred that prostate tumours frequently are delineated incompletely or that normal tissue is included in tumour areas. This will have implications for the outcome of focal boosting strategies and of focal therapy, which is an upcoming and promising treatment strategy.

In the present study, we searched for a histological explanation of the difficulty to detect all tumour voxels. We showed a significant difference in CD and MVD between detected (true positives) and non-detected tumour parts (false negatives). False-negative tumour voxels contain on average a lower density of cells and microvessels (Figure 3a and 3b). Interestingly, the false-negative tumour voxels show CDs which are similar to the values found in the false positives. Furthermore, MVDs in false-negative tumour voxels are similar to the MVDs found in non-tumour PZ tissue. This strongly indicates that the limitations in sensitivity and specificity of tumour voxel detection with MRI are caused by the underlying histology. MRI-based tumour prediction models might therefore reflect underlying histological characteristics like cell density and microvessel density, rather than predicting tumour presence.
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Figure 3. Cell density (a) and microvessel density (b) for MR-detected (true positives) and non-detected tumour (false negatives) voxels and for peripheral zone tissue assigned as tumour (false positives) and non-tumour (true negatives) based on MR images. Significant differences (p < 0.0001) are marked with an ‘*’.

[15]. Although this may be seen as a disadvantage, when it comes to radiotherapy, this reflection of histological characteristics may be beneficial. In contrast to all-or-nothing therapies like surgery, in radiotherapy it is possible to sculpt the radiation dose based on underlying tissue characteristics to obtain optimal tumour control probability [16]. A model reflecting histological properties may therefore be a valuable input for such an approach.

Figure 4. Percentage of true-positive and false-negative tumour voxels for the different Gleason scores. We found a trend that the tumour voxels with higher Gleason score (GS ≥ 3 + 4) score were easier to detect (p = 0.06). N, total amount of voxels per Gleason score.

For translation of histological variables into prescription of radiation dose, one could argue from a radiobiological point of view, that tumour regions with a higher CD require higher radiation dose levels [17]. The relation between MVD and required dose is, however, more complicated. In many cancers, high vascularity has been associated with tumour growth and metastases. In prostate cancer, this relationship is controversial. Schlemmer et al. reported in a study including 28 patients, no correlation between MVD and GS and other clinical variables [10]. On the other hand, in a study by Mucci et al. including 572 patients, high-grade prostate tumours showed significantly larger MVD than low-grade tumours [18]. This is consistent with what we found in the current study. Future studies are necessary to investigate the relation between imaging parameters and histological variables on one side and required dose levels on the other side.

We found a trend that tumour voxels with higher GS were easier to detect. This suggests that the most
aggressive tumour parts are the most easy to detect. In addition, of voxels with GS3 + 3, 85% was detected in this study. This is a high value compared with other studies [12]. It can be speculated that the histology of the detected GS3 + 3 voxels is slightly different from the non-detected voxels. However, the number of patients in this study is too small to draw definitive conclusions on this.

In this study, detailed histological properties are related to MR parameter maps on voxel level. Such high resolution information about the relation between MRI and histology is important for precise target definition for focal boosting and focal therapy. Previous studies have shown relationships between histology and MR parameter maps. Regions with a higher CD are correlated with low ADC and high $K^{\text{trans}}$ values [9,19]. Tumour CD was related to detectability based on ADC images [12]. Qualitative parameters retrieved from the analysis of DCE-MRI signal-enhancement curves have been related with microvasculature of prostate tumour tissue [10,11]. However, most of these studies were performed on a regional or tumour level and did not provide the detailed information which is required for focal treatment. Therefore, focus in this study was on the voxel level. In addition, most studies did not investigate the non-tumour PZ tissue in a detailed fashion. We showed that non-tumour PZ tissue is highly heterogeneous on CD and MVD. This may be partly caused by prostate intraepithelial neoplasia and prostatitis, but even healthy PZ tissue is highly heterogeneous on these characteristics.

This study shows that tumour voxels with a CD below 3000 cells/mm² and a MVD less than 90 vessels/mm² are harder to detect. Given the high similarity in CD and MVD between tumour and healthy tissue (Figure 3a and b), it seems unlikely that all tumour voxels can be detected using the imaging techniques DWI and DCE-MRI, unless large volumes of non-tumour tissue are included. This is, of course, not endeavoured by focal boosting strategies or focal therapy. As tumour detection is still not perfect, focal boosting might be preferred above focal therapy, as with focal boosting the remaining prostate tissue receives normal dose levels. Local recurrences will be reduced, toxicity, however, will stay at same levels.

This study has some limitations. First of all, the number of patients is small. The explorative nature of this work should be kept in mind for the interpretation of the results. Due to the small registration error, we were able to relate histopathological information with MR images in a highly detailed fashion. This high-resolution comparison resulted in a high number of voxels included in this study. However, one should keep in mind that all these voxels are not completely independent. Moreover, $K^{\text{trans}}$ values were normalised to the median values in the PZ. This method is feasible, unless > 50% of the PZ is comprised of tumour. In the future, improved quantification of DCE-MRI might allow the use of absolute $K^{\text{trans}}$ values [20]. Unfortunately, the phase images needed for this quantification method, were not available in this patient cohort. Furthermore, this study focused only on the PZ of the prostate. This has several reasons. First, the number of transition and central zone tumours in our patient group was limited (n = 1). Second, the interpretation of MRI is a lot more complicated in these parts of the prostate, due to the presence of benign prostatic hyperplasia. Additionally, histological data was retrieved from patients of the same cohort as used for the initial validation of the model. To extend the applicability of the model to other institutes, the model accuracy is being validated in an independent patient cohort. Finally, in this study, we compared model outcome with the tissue characteristics CD and MVD. However, these tissue characteristics do not fully explain the large spread in the ADC and $K^{\text{trans}}$ data. An explanation for this might be the limited measurement precision of ADC and $K^{\text{trans}}$. Moreover, future research should focus on what tissue characteristics explain ADC and $K^{\text{trans}}$ values inside tumour tissue best. The ADC, for instance, might be influenced by other factors like extracellular and intracellular space and volume, as well as membrane permeability [21].

In conclusion, we found large heterogeneity inside prostate tumours and non-tumour PZ tissue on histological level. This heterogeneity is reflected by the MR images. CDs and MVDs of false-negative tumour voxels resembled those found in non-tumour PZ tissue. This illustrates that the limitations in tumour voxel detection with MRI are related to histological characteristics. In addition, detected tumour voxels had high CDs and MVDs and voxels with higher GS showed a trend towards easier detection. As stated before, high CDs require higher radiation doses to sterilise a tumour and high MVDs may be related to tumour aggressiveness. Therefore, it could be speculated that the tumour parts requiring the highest radiation dose are detected with MRI and can be treated using focal therapy or focal boosting.

**Acknowledgements**

This research was financially supported by the Dutch Cancer Society Grant No. UU-2009-4310.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
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Supplementary material available online
Supplementary Appendix 1