Computerized analysis of prostate lesions in the peripheral zone using dynamic contrast enhanced MRI

Pieter C. Vos, Thomas Hambrock, Christina A. Hulsbergen - van de Kaa, Jurgen J. Fütterer, Jelle O. Barentsz, and Henkjan J. Huisman

Department of Radiology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 18, 6525 GA Nijmegen, The Netherlands

(Received 24 April 2007; revised 10 December 2007; accepted for publication 18 December 2007; published 13 February 2008)

A novel automated computerized scheme has been developed for determining a likelihood measure of malignancy for cancer suspicious regions in the prostate based on dynamic contrast-enhanced magnetic resonance imaging (MRI) (DCE-MRI) images. Our database consisted of 34 consecutive patients with histologically proven adenocarcinoma in the peripheral zone of the prostate. Both carcinoma and non-malignant tissue were annotated in consensus on MR images by a radiologist and a researcher using whole mount step-section histopathology as standard of reference. The annotations were used as regions of interest (ROIs). A feature set comprising pharmacokinetic parameters and a T1 estimate was extracted from the ROIs to train a support vector machine as classifier. The output of the classifier was used as a measure of likelihood of malignancy. Diagnostic performance of the scheme was evaluated using the area under the ROC curve. The diagnostic accuracy obtained for differentiating prostate cancer from non-malignant disorders in the peripheral zone was 0.83 (0.75–0.92). This suggests that it is feasible to develop a computer aided diagnosis system capable of characterizing prostate cancer in the peripheral zone based on DCE-MRI. © 2008 American Association of Physicists in Medicine. [DOI: 10.1118/1.2836419]

Key words: computer aided diagnosis, prostate, magnetic resonance imaging, pharmacokinetic modeling

I. INTRODUCTION

It is estimated that one out of ten male cancer deaths in 2007 will be caused by prostate cancer (PCa). Furthermore, with a total of 218,890 cases, PCa is the most common non-cutaneous cancer in the United States. PCa incidence rates continue to increase, although at a slower rate than those reported for the early 1990s and before. This trend may be attributable to increased screening through prostate-specific antigen (PSA) testing as well as the aging of the population. The definitive diagnosis of PCa is most often established through transrectal ultrasound (TRUS)-guided sextant biopsy.

For men diagnosed with prostate cancer, a number of treatment options exist, with differing side effects. The therapeutic options are mostly determined using nomograms of which the Partin tables are most commonly used. The Partin tables estimate the chance of organ-confined disease, seminal vesicle invasion and lymph node metastasis, based on the result of digital rectal examination, biopsy Gleason score and PSA value. However, these clinical assessments are not accurate in determining the local stage. Elevated PSA levels can be observed in non-malignant disorders such as prostatitis or benign prostatic hyperplasia (BPH). The limitations of sextant biopsy are increasingly recognized, which has provoked interest in multimodal magnetic resonance imaging (MRI) as an alternative method of tumor evaluation. Accurate staging is important for a proper disease management. Curative therapy is only effective in cases of organ confined (surgical candidate) PCa, whereas androgen therapy and/or radiotherapy are more effective in advanced disease. Accurate localization is important for evaluation of the tumor location and the distance to the neurovascular bundle and prostate capsule, to determine if a nerve sparing operation is possible, or assist the planning of intensity-modulated radiotherapy.

MRI localization can reduce the number of repeat biopsies, improve the staging performance and guide surgery or radiotherapy. T2-weighted MRI using a pelvic phased-array coil can visualize the prostate including the surrounding anatomy and depict tumor suspicious areas of low signal intensity within a high-intensity peripheral zone. An endorectal coil improves the spatial resolution, resulting in better anatomical visualization which may result in an improved diagnostic accuracy of the localization and staging of PCa. However, in addition to PCa, the differential diagnosis of a low signal intensity area includes post-biopsy hemorrhage, prostatitis, BPH, effect of hormonal or radiation treatment, fibrosis, calcifications, smooth muscle hyperplasia and fibromuscular hyperplasia.

Dynamic contrast-enhanced MRI (DCE-MRI) can be used as an additional tool to visualize PCa (neo-) vascularity and interstitial space. Due to the high vascularity, increased capillary permeability as well as interstitial hypertension in tumors, DCE-MRI shows better distinction between malignant lesions and normal tissue compared to conventional MRI alone. Fütterer et al. showed that using T2-w images in combination with DCE-MRI for localizing PCa, equal or
greater than 0.5 cm³, resulted in an accuracy of 81%–91% whereas using T2-w MR images alone resulted in a localizing accuracy of 68%.

Post-biopsy hemorrhage, prostatitis and BPH can all mimic PCa enhancement patterns, thus comprising the specificity of the technique. Another major obstacle to the application of MRI analysis in the routine clinical practice of prostate imaging is the variability of interpretation criteria and absence of interpretation guidelines.²³ Our study aims to increase the objectivity and reproducibility of prostate MRI interpretation by developing a computer aided diagnosis (CAD) system.

The proposed method enables an objective automated quantification and classification of features to discriminate between benign and malignant lesions, and may improve the tumor localization accuracy of the radiologist. In addition to objective analysis, computerized analysis can take full advantage of information across slices in three-dimensional (3D) multi-feature data sets which is difficult to assess visually from individual images. CAD has been successfully pursued in other diagnostic areas such as mammography,²⁴ computed tomography (CT) chest²² as well as breast MRI.²³ In the field of the prostate, Chan et al. constructed a summary statistical map of the peripheral zone based on the utility of multichannel statistical classifiers by combining textural and anatomical features in PCa areas from T2-w images, diffusion weighted images, proton density maps, and T2 maps. Madabhushi et al. generated similar statistical maps based on T2-w images using histological maps as ground truth and showed the additional value of combining features. However, to our knowledge, there have been no reported studies about similar work on PCa using DCE-MRI.

The purpose of this study was to investigate the feasibility of a CAD system capable of objectively discriminating PCa from non-malignant disorders located in the peripheral zone of the prostate. Localizing PCa in the central gland of the prostate is considered difficult because this area is often affected by BPH, which can have areas of low signal intensity on T2-w images and shows enhancement patterns in DCE-MRI similar to that of PCa. Nevertheless, 65%–74% of the prostate tumor nodules are located in the peripheral zone and central gland tumors are often less aggressive.¹⁰ The focus of this study is therefore on the peripheral zone of the prostate.

II. METHODS

The proposed CAD method is based on a typical CAD setup illustrated in Fig. 1 and works as follows: A prostate MRI exam is visualized as described in Sec. II A. While interpreting the images, the radiologist can delineate a lesion as a region of interest (ROI) in the images, using a method discussed in Sec. II B. From here the characterization of the ROI is fully automated. The CAD system extracts a relevant feature set from the ROI as explained in Sec. II C. The extracted set of features is presented to a trained classifier which calculates the malignancy likelihood for the lesion as described in Sec. II D. Finally, the calculated likelihood is presented to the radiologist to assist in his or her diagnosis. The CAD system was implemented in an open source programming environment, The Visualization ToolKit using the Tool Command Language and C++.

II.A. Volume visualization

The CAD program can visualize multimodal MR volumes I_k, where k=1…K and K is the number of image volumes. The set of K volumes comprises all the volumes acquired in a MR study plus derived volumes from the acquired volumes. Examples of acquired volumes are T2-w images and T1-w images. Additionally, descriptive parameter maps derived from DCE T1-w images by means of pharmacokinetic modeling are computed (see Appendix for a description on pharmacokinetic modeling). In each view all available volumes can be rendered either as background or as transparent color coded overlays. The cursor is positionable in one of the views with the mouse after which the CAD system will instantly update the location in all views. Although the MR data are obtained in slices, the CAD system visualizes the data as 3D volumes taking all directions into account. Figure 2 demonstrates the CAD system with a dedicated prostate hanging protocol as it is used in our clinic for localizing PCa.

II.B. Lesion segmentation

A 3D drawing tool has been implemented which allows the user to easily delineate a suspicious lesion in 3D. At the request of the user a 3D sphere shaped ROI is added at the position of the cursor and visualized in all views. It is adjustable in size to fully delineate the suspicious area. The intended use is to adjust the sphere to be large enough to fully include the lesion’s size, as to reduce inter-observer variability (see Sec. II C).

Let a ROI Sᵢ define a set of N Cartesian voxel locations xᵢ in the MR coordinate system

\[ Sᵢ = \{x₁, x₂, \ldots, x_N\} \] (1)

Let \( V_{r,k} \) represent a set of scalar values in image volume I_k, identified by \( Sᵢ \)

\[ V_{r,k} = \{V_k(x_i) | x_i \in Sᵢ\} \] (2)

The assumption is that all image volumes I₁, I₂, …, I_k are registered to each other in the MR coordinate system and, as
a result, a lesion segmentation in $I_k$ will segment the same lesion area in $I_{k+1}$, regardless of the image resolution or orientation.

II.C. Feature extraction

A reduced feature set $F_r$ is calculated from the scalar values of the available volumes ($V_{r,k}$). Each feature in the feature vector $F_r = \{f_1, f_2, \ldots, f_L\}$, with $L$ the number of features, is a first-order statistic of the scalar values of volume $I_k$. One of these statistics is the 25% or 75% percentile. These percentiles are especially suited for volumes that show an heterogeneous pattern, e.g., the derived volume $K_{\text{trans}}$. This heterogeneity is most common for tumor and differs from normal tissue and benign lesions. The 25% or 75% percentile will differ more from the average value when hotspots are present and will give an estimate of the value in that hotspot, as demonstrated in Fig. 3. This heterogeneity is also recognized by the pathologist (at macro scale). They base a histological grade on the Gleason system, in which the dominant and secondary glandular histological patterns are determined. By segmenting the whole lesion and using percentiles to extract the hotspot, variability among users is reduced. Stoutjesdijk et al. showed that manual selection of the hotspots is the major source of variation in the interpretation of the DCE characteristics of breast MRI lesions. Thus, annotating the whole enhancing region instead of just the hotspot and automatically extracting the features sensitive to hotspots within the region, makes the technique more reproducible. An additional advantage of using percentiles is that it is less sensitive to extreme values.

To do so, $V_{r,k}$ is summarized into a single scalar value $f_{r,k,p}$ by calculating its percentile $p$

$$H_{r,k}(f_{r,k,p}) = p,$$

where $H_{r,k}$ is the cumulative density histogram of the scalar values in $V_{r,k}$.

II.D. Classification

The final step of the CAD program is to combine the computed features and to estimate the likelihood of malignancy of the region of interest. The malignancy likelihood $l_r$ is calculated using a trained classifier $\tau$

$$l_r = \tau(F_r; T),$$

where $T$ is a training set of feature vectors and truth states. Classification was performed using support vector machine.
SVM analysis on the feature set provided by the statistical package R. SVMs are currently widely used in similar problems as they can act as a general purpose non-linear classifier. SVMs have been shown to perform well on various datasets of limited size. SVMs map input vectors to a higher dimensional space where a maximal separating hyperplane is constructed by means of a kernel function. For this study the radial basis function kernel $K(u,v) = \exp(-\gamma |u - v|^2)$ with parameter $\gamma = 1/5$ (5 equals the number of features used) was chosen and the cost of constraints violation (or “C” constant of the regularization term in the Lagrange formulation) was set to 1. When the classifier has calculated $l_\tau$, the user is prompted with the estimate of the likelihood of malignancy as shown in the example in Fig. 7(c).

### III. FEATURE DESCRIPTION

The following features were extracted from $S_e$.

- **50% T1Static**: The T1Static parameter is the pre-contrast static value of the T1 estimate of the longitudinal relaxation rate in ms. T1-weighted signals are not ideally suitable for use in quantitative assessment of contrast media concentration. We therefore use dynamic T1 mapping with snapshot FLASH sequences as a direct approach to quantification, as described in Hittmair et al. If a post-biopsy hemorrhage is present, it is clearly visible as a high-intensity area on a T1-w image. The biopsy hemorrhage is often visible as a large homogeneous area, hence the median is used to capture this.

- **75% V_e**: In the extravascular, extracellular space (EES) of normal tissue, pressure is near atmospheric (25 mm Hg) values, whereas in tumors it may reach 50 mm Hg or even more. The interstitial hypertension may be due to increased vascular permeability in combination with a lack of lymphatic drainage due to the absence of functional lymphatic vessels within the tumor itself. This results in an increase of the EES. The EES is therefore considered a very descriptive parameter defined as percentage per unit volume of tissue.39

---

**Fig. 3.** A prostate cancer case to demonstrate the rationale for using percentiles. Although both regions do not differ much in their median, the tumor shows a wide spectrum of heterogeneity in their dynamic enhancement patterns and has more high values. Subfigure 3(a) shows a transverse T2-w view of the prostate with a transparent $K^{\text{trans}}$ color-coded overlay. The bi-lateral enhancement in the peripheral zone are both suggestive of cancer. In subfigure 3(c) a histogram distribution of the malignant lesion is shown, located in the right peripheral zone (solid box) and correlated to tumor 1 with Gleason 4+4 in the corresponding histopathology slice shown in subfigure 3(b). The 75% percentile is 0.36. Note the wide spectrum. Subfigure 3(d) shows a histogram distribution of a suspicious enhancing normal peripheral zone region (dotted box). The 75% percentile is 0.23. Note the narrow spectrum.
Interstitial leakage space at tumor hotspots can be three to five times larger than normal tissue, hence the upper quartile is used to capture these hotspots.

75% $k_{ep}$ & $K_{trans}$. The transfer constant ($K_{trans}$) and rate constant ($k_{ep}$) both have units 1/min, where $K_{trans}$ relates to permeability surface area. The permeability (or leakiness) surface area refers to the ability of tracer molecules to pass through interendothelial fenestrae and junctions into the interstitial compartment. High permeability of the vasculature is a characteristic of pathological blood vessels in inflamed tissues and tumors. In case of a tumor, both $K_{trans}$ and $k_{ep}$ often show focal enhancement. The upper quartile captures the presence of hotspots.

25% late wash: The late wash parameter quantifies the slope of the curve after the first wash-in phase. Although it does not directly correlate to physiological parameters, the presence of washout is highly indicative of PCa, and does not directly correlate to physiological parameters, the slope of the curve after the first wash-in phase. Although it does not directly correlate to physiological parameters, the slope of the curve after the first wash-in phase.

IV. TRAINING AND EVALUATION

IV.A. Dataset

The study set consisted of 34 consecutive patients that were selected in a previous study of Fütterer et al. These patients had biopsy-proven PCa and underwent DCE-MRI imaging at 1.5 T, complementary to the routine staging MR imaging examination of the prostate. Patients were included (between April 1, 2002, and June 1, 2004) in the study only if they were candidates for radical retropubic prostatectomy within six weeks after MR imaging. The study of Fütterer et al. was approved by the institutional review board, and informed consent was obtained from all patients prior to MR imaging. After imaging, all patients underwent radical retropubic prostatectomy. Exclusion criteria were: Previous hormonal therapy, lymph nodes positive for metastases at frozen section analysis, contra-indications to MR imaging (e.g., cardiac pacemakers, intracranial clips), contra-indications to endorectal coil insertion (e.g., anorectal surgery, inflammatory bowel disease). The mean prostate specific antigen level was 8 ng/ml (range, 3.2–23.6 ng/ml), mean Gleason score was 6.1 (range, 5–8). MRI was performed on average three weeks after transrectal ultrasonographically guided sextant biopsy of the prostate.

IV.B. MR acquisition

Images were acquired with a 1.5 T whole body MR scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). A pelvic phased-array coil as well as a balloon-mounted disposable endorectal surface coil (MedRad®, Pittsburgh, PA) was inserted and inflated with approximately 80 cm$^3$ of air, were used for signal receiving. The machine body coil was used for rf transmitting. An amount of 1 mg of glucagon (Glucagon®, Novo Nordisk, Bagsvaerd, Denmark) was administered directly before the MRI scan to all patients, to reduce peristaltic bowel movement during the examination.

The protocol for acquisition consisted first of a localizer and two fast gradient spin-echo measurements for patient and coil positioning. Thereafter high-spatial-resolution T2-weighted fast spin-echo imaging in the axial, sagittal and coronal planes, covering the prostate and seminal vesicles, was performed. The frequency encoding direction was anteroposterior to increase the acquisition speed.

Third, 3D T1-weighted spoiled gradient echo images were acquired before and during an intravenous bolus injection of...
paramagnetic gadolinium chelate (0.1 mmol/kg, gadopentetate, Magnesin®; Schering, Berlin, Germany) using a power injector (Spectris, Medrad®, Pittsburgh, PA) with an injection rate of 2.5 ml/s followed by a 15 ml saline flush. At these settings a 3D volume with ten partitions, covering the whole prostate, was acquired every 2 s for 120 s. Before contrast injection the same axial 3D T1-weighted gradient echo sequence was used to obtain proton density images and identical positioning to allow calculation of gadolinium chelate concentration curves. See Table I for the specific acquisition parameters. Within three weeks of biopsy, there can be postbiopsy artifacts on MRI. This cannot be avoided as we feel it is unethical to unnecessarily delay a scheduled prostatectomy. The optimal timing of post-biopsy MR Imaging of the prostate has been researched by Ikonen et al. and White et al. They advise deferring MR imaging for at least three weeks after biopsy.

IV.C. ROI annotation

IV.C.1. Histopathological analysis

All patients underwent radical retropubic prostatectomy. The prostatectomy specimens were fixed overnight (10% neutral-buffered formaldehyde) and coated with India ink. Axial whole mount step sections were made at 4 mm intervals in a plane parallel to the axial T2-w images and routinely embedded in paraffin. Tissue sections of 5 µm were prepared and stained with haematoxylin and eosin. An experienced pathologist (C.H.V.D.K.) who was blinded to the imaging results, established malignancy from microscopy. Regions of malignancy were outlined on digital microscopic whole-mount images from a charge coupled device camera. Figure 7(d) shows an example of an histopathological map.

IV.C.2. Annotation in the MRI data

The whole-mount step-section histology tumor maps were used as ground truth for training and evaluating the performance of the CAD system. The morphology of the central gland, peripheral zone, cysts, calcifications, and urethra were used as landmarks to find the corresponding MRI slice. Aligning MR slices to whole-mount step sections is considered difficult, it is subjective and the section thickness used in the MR imaging sequences can be different. To overcome these problems a method was developed that semiautomatically matches MR slices to the step sections of histopathology. The method has the following setup: One of the views is set to a 3D rendering mode for volumes. In this mode the volume is rendered in three planes in all directions. The planes can be manipulated to move through the volume slices. In this 3D view a default 3D ellipsoid is rendered as a transparent surface. The goal is to fit the prostate roughly by interactively resizing and translating the ellipsoid. The cross sections of the ellipsoid are simultaneously displayed in the two-dimensional views for a more accurate result. The final ellipsoid is then divided in the same number of slices as the prostatectomy specimen was cut. By doing this, the specimen images are aligned to the T2-w images. See Fig. 4 for a demonstration.

The anatomy of the prostate is best imaged on T2-w images which were therefore used for correlating the histopathological map. The features used for this experiment, however, were extracted from T1-w images. Because the patient may have moved and no registration is applied to correct for patient movement, the pre-contrast T1-w images were semitransparently overlaid on the T2-w images, to allow for visual inspection and comparison for anatomic mismatch due to patient related movements. If a mismatch was evident, it was compensated for by correcting the annotation on the pre-contrast T1-w images, thereby avoiding the annotation of periprostatic vasculature and urethra.

A region of interest (ROI) was placed to cover the whole lesion volume based on histopathology. After a thorough inspection of the segmentation, the ROI was saved to disk along with a classification label N, NS or M. The definitions of the labels are given in Table II.

For all saved ROIs Sj, with one of the assigned labels N, NS or M, information was summarized by collecting the features 

\[
F = \{ f_{r,K_{\text{trans}}}, f_{r,K_{\text{proj}}}, f_{r,K_{\text{trans}}}, f_{r,K_{\text{proj}}}, f_{r,V_{\text{r}}}, f_{r,V_{\text{sagittal}}}, f_{r,V_{\text{transverse}}}, f_{r,T1_{\text{static}},50} \} \tag{5}
\]

IV.D. ROC analysis

The discriminating performance of the CAD system was estimated by means of the area under the receiver operator characteristics (ROCs) curve (AUC). Let \( \xi = (l_1, l_2, \ldots, l_m) \) be the vector of calculated malignancy likelihoods for m ROIs with the trained classifier \( \tau \). The ROIs are split into two groups \( \alpha \) and \( \beta \). Let \( \gamma_{\alpha} = \{ j | q_j \in Q_\alpha \} \) and \( \gamma_{\beta} = \{ j | q_j \in Q_\beta \} \) be the corresponding vectors of indices, where \( Q_\alpha \) and \( Q_\beta \) are disjoint and subsets of \( Q \) (see Table II) for a definition of the labels). The AUC for the classification performance between two subsets of ROIs identified by \( \gamma_{\alpha} \) and \( \gamma_{\beta} \) is given by

\[
AUC_{\gamma_{\alpha}\gamma_{\beta}} = \frac{\Sigma_{j \in \gamma_{\alpha}} \Sigma_{j' \in \gamma_{\beta}} \phi(l_j, l_{j'})}{\eta_{\gamma_{\alpha}} \eta_{\gamma_{\beta}}}, \tag{6}
\]

with kernel function.
When looking at the scatterplots of Fig. 5 a noticeable clustering of features is seen. The scatterplots demonstrate that the feature values are usable to characterize lesions as \( M, NS \) or \( N \). It can be observed that the \( N \) regions are compact and well clustered. Although the regions of type \( NS \) and \( M \) show a larger spread, they are still clustered and can thus be differentiated. Furthermore, the \( NS \) regions appear to be more clustered than the \( M \) regions.

The localization performance of the discrimination between \( \{ N, NS \} \) and \( \{ M \} \) is demonstrated in the ROC curve shown in Fig. 6(a). The figure shows that the diagnostic accuracy (AUC\(_{loc}\)) was 0.92 [95% confidence intervals = 0.87–0.97]. In Fig. 6(b) the discriminating performance between \( \{ NS \} \{ M \} \) regions is demonstrated. The diagnostic accuracy (AUC\(_{dif}\)) in this case was 0.83 [95% confidence intervals = 0.75–0.92]. The ROC curves show that the performances are statistically better than chance.

Figure 7 presents a true-positive case as well as a true-negative case: In both the transverse and coronal views of the prostate, a bilateral enhancement is seen in the peripheral zone when overlaying several parametric maps on the T2-w images. Because of the enhancement, both sides are suspicious for cancer. The CAD system, however, calculated a likelihood of malignancy of 80% for the annotated region that was identified as PCa by histopathology. In the other region, the CAD system calculated a likelihood of 20% of being malignant. Additionally, histopathology confirmed that there was no evidence for tumor at the specific location.

VI. DISCUSSION

This study showed that it is feasible to develop a CAD system capable of discriminating PCa from the normal peripheral zone and non-malignant disorders with a diagnostic accuracy of 0.92 (0.87–0.97). It was also shown that it is possible to develop a more clinically relevant CAD system, where the radiologist typically is only interested in abnormal enhancing areas. For the discrimination of solely non-malignant suspicious enhancing (NS) areas from PCa in the peripheral zone, a diagnostic accuracy of 0.83 (0.75–0.92) was obtained. This CAD system thus has the potential of being a valuable, additional diagnostic aid.

### V. RESULTS

Of the 34 patient studies, four were excluded because of insufficient dynamic data caused by patient movement or coil artifacts. In total 39 \( M \) regions were annotated in the peripheral zone. The number of \( NS \) regions annotated in the peripheral zone was 21. The number annotated \( N \) regions was 30.

### TABLE II. The three classification types of \( Q \) that were assigned to the annotated regions.

| \( N \) (normal) | Region of normal enhancement and histopathological analysis showed no evidence for tumor. |
| \( M \) (malignant) | Histopathology confirmed tumor with a clinical relevant diameter of at least 5 mm. Regions with prostatic intraepithelial neoplasia (PIN) were excluded because they are considered to be a precursor of PCa. |
| \( NS \) (non-malignant suspicious enhancing) | Region of non-malignant suspicious irregular heterogeneous enhancing areas where the underlying histopathological analysis showed no evidence for tumor. Region with histopathological confirmed prostatitis. Region of post-biopsy hemorrhage without any histopathological evidence for tumor. |

Reference 45.
The proposed CAD method has some similarity with the study of Fütterer et al. \(^\text{10}\) In their study, it was shown that when using T2-w images and DCE-MRI in localizing PCa, radiologists achieved an overall accuracy of 0.92, when discriminating PCa pre-assigned regions from normal peripheral zone and non-malignant disorder pre-assigned regions. Although the focus of this study was the normal peripheral zone of the prostate, similar regions were used for the characterization by the CAD system. Furthermore, the same patient database was used. Our CAD method, on the contrary, was trained with primarily pharmacokinetic features, whereas the radiologist used the T2-w images as an additional feature of region characterization.

The results of this study demonstrate for the first time in an objective manner that including DCE-MRI can discriminate PCa from NS areas in the peripheral zone. This is supported by former studies where human observers concluded the same. \(^{12\text{–}19,46,47}\)

Histological correlation with MR images is recognized to be an imperfect gold standard for a number of reasons. These include: Errors in registering the location of the imaging sections with histological slice specimens, inaccuracies resulting from tissue shrinkage secondary to fixation and errors due to partial volume averaging effects. \(^{14,43,48}\) In most studies the number of slices is simply counted taking the shrinkage into account and using the morphology of the central gland, peripheral zone, cysts, calcifications, and urethra as landmarks.
they did not create a CAD system capable of calculating a malignancy likelihood, they did evaluate the discriminating performance of the kinetic parameters. Their best performing parameter, early degree of enhancement, achieved an AUC of 0.81. This result can be compared to our localizing classifier $AUC_{loc}$ of 0.92. The difference in performance can be attributed to the method that was chosen to calculate the pharmacokinetic parameters. Kiessling used the method proposed by Brix et al.\textsuperscript{50} where a fixed arterial input function for every patient is assumed (fixed calibration), whereas in this study the reference tissue model (per patient calibration) was used (see the Appendix).

In a previous study\textsuperscript{51} we showed that a per patient calibration indeed has a positive effect on the discriminating performance of PK parameters over a fixed calibration.

Chan et al.\textsuperscript{25} describe the only in-vivo CAD system that provides an estimated malignancy likelihood by combining information from T2-weighted, T2-mapping, and line scan diffusion images. They achieved a diagnostic performance of 0.84. This can be compared to our $AUC_{loc}$ of 0.92. The lower performance is likely attributed to the lack of DCE-MRI features. Moreover, we have also researched and demonstrated the ability of our method to discriminate suspicious enhancing benign regions from malignant regions. The latter is of even greater importance in actual clinical conditions.

The current study has a number of limitations. The CAD system is not fully automated, since the user needs to identify normal peripheral zone for calibration with the reference tissue method (see the Appendix). As a result, the healthy tissue needs to be annotated in advance, which could result in the annotation of PCa, which makes the CAD system not clinical usable. An automated calibration technique makes the CAD system fully automated and is being researched. The effect of user-variability in annotating the ground truth on the performance has not been researched.

In conclusion, this study demonstrated the possibility of developing a CAD system capable of objectively discriminating malignant lesions from NS areas located in the normal peripheral zone of the prostate with an accuracy of 0.83 [95% confidence intervals=0.75–0.92]).

**ACKNOWLEDGMENTS**

This work was funded by Grant No. KUN 2004-3141 of the Dutch Cancer Society.

**APPENDIX: DCE-MRI POSTPROCESSING AND PHARMACOKINETIC MODELING**

All MRI data were transferred to an independent workstation with in-house build software. Each MR signal enhancement-time curve was first fitted to a general exponential signal enhancement model as described previously.\textsuperscript{12} This reduces a curve to a five parameter model: Baseline ($s_0$); start of signal enhancement ($t_0$), which defines the onset of the exponential curve; time-to-peak ($\tau$), the exponential constant; peak enhancement ($s_p$), the signal amplitude at which the exponential curve levels off; and late wash, defined as the slope of the late part of the exponential curve.
The reduced signal enhancement-time curve was converted to a reduced tracer concentration [mmol/ml]-time curve effectively converting $s_p$ to $C_{gd,p}$. We have implemented the method such that in an intermediate step the T1 estimates are computed. The T1Static parameter is the baseline T1 estimate ($s_0$) prior to contrast enhancement.

Analysis of DCE-MRI data is usually based on the indicator dilution theory and requires knowledge of the concentration of the contrast agent in the blood plasma. Without any calibration, inter-patient plasma profile variability causes fluctuations in PK estimates, which are not related to the tissue condition. When using a power injector the most likely cause of plasma curve differences is the patient itself, e.g., differences in body weight (total distributional volume), heart rate, vascular condition. Removing the plasma shape can be regarded as a form of patient calibration. Among the wide variety of techniques for estimating plasma profiles, we have chosen for the reference tissue method and experienced robust results with the technique. The reference tissue method assumes that a tissue area within the patient is available with a known tissue model based on literature values. By doing a deconvolution the actual tissue im-

![Fig. 7. Example of two regions in the peripheral zone of the prostate that are difficult to differentiate. A bi-lateral enhancement is seen with pharmacokinetic parameters, suggesting that both sides are suspicious of prostate cancer. For both regions the CAD system calculated the likelihoods of malignancy using the classifier with a diagnostic accuracy (AUC_lo) of 0.92. Subfigure 7(a) shows a transverse T2-w image of the prostate with $V_c$ color overlay map. Note the bilateral enhancement of the peripheral zone, which makes both sides suspicious for cancer. Subfigure 7(b) shows a coronal T2-w image of the prostate with $K_{trans}$ color overlay map. This parameter also shows a bi-lateral enhancement, suggesting the presence of tumor at both sides. Subfigure 7(c) the CAD predicted likelihoods of the annotated regions in the left and right peripheral zone are shown. The green area summarizes the distribution of all the calculated likelihoods for all $N$ and $NS$ regions from the database used for training the classifier. The red area summarizes the smoothed distribution of all the calculated likelihoods for all $M$ regions from the database used for training the classifier. The areas are smoothed using a two-dimensional nonlinear variable span smoother based on local linear fits, in which local cross-validation is used to estimate the optimal span. The black lines are the calculated likelihoods of malignancy for the regions. The dotted line corresponds with the region in the left of the peripheral zone (with a predicted malignancy likelihood of 80%). The solid line corresponds with the region in the right of the peripheral zone (with a predicted malignancy likelihood of 20%). Histopathology confirmed the adenocarcinoma in the left peripheral zone (subfigure 7(d)). The tumor was staged as T2b and with a Gleason score of 3+3. ]
pulse response can be determined. Deconvolution of the plasma profile and estimation of pharmacokinetic parameters conforms to the theoretical derivations but is implemented in the reduced signal space as shown in the following equation:

\[
V_e = \frac{C_{\text{gd-pplasma}}}{C_{\text{gd-pplasma}}},
\]

where \(V_e\) is an estimate of the extracellular volume [%], \(K_{\text{trans}}\) the volume transfer constant [1/min], and \(k_{\text{ep}}\) the rate constant [1/min] between extracellular extravascular and plasma space. The subscript “tissue” stands for a measurement in the tissue under investigation and subscript “plasma” for the reference tissue plasma estimates based on literature values. The reference tissue was determined by selecting manually a set of voxels in the healthy (normal) peripheral zone using whole mount section histopathology as guidance.

\[
k_{\text{ep}} = \frac{1}{\tau_{\text{tissue}} - \tau_{\text{plasma}}},
\]

\[
K_{\text{trans}} = V_e - k_{\text{ep}},
\]

where \(V_e\) is an estimate of the extracellular volume [%], \(K_{\text{trans}}\) the volume transfer constant [1/min], and \(k_{\text{ep}}\) the rate constant [1/min] between extracellular extravascular and plasma space. The subscript “tissue” stands for a measurement in the tissue under investigation and subscript “plasma” for the reference tissue plasma estimates based on literature values. The reference tissue was determined by selecting manually a set of voxels in the healthy (normal) peripheral zone using whole mount section histopathology as guidance.

\[\tau_{\text{tissue}} = \frac{1}{k_{\text{ep}}}.\]

where \(V_e\) is an estimate of the extracellular volume [%], \(K_{\text{trans}}\) the volume transfer constant [1/min], and \(k_{\text{ep}}\) the rate constant [1/min] between extracellular extravascular and plasma space. The subscript “tissue” stands for a measurement in the tissue under investigation and subscript “plasma” for the reference tissue plasma estimates based on literature values. The reference tissue was determined by selecting manually a set of voxels in the healthy (normal) peripheral zone using whole mount section histopathology as guidance.

\[\tau_{\text{tissue}} = \frac{1}{k_{\text{ep}}}.\]


