

Computer-aided Diagnosis of Prostate Cancer: Clinical Utility of Integrating Model-free and Kinetic-based Analysis of High Spatial Resolution Dynamic Contrast Enhanced 3 Tesla MRI.

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Purpose: The goal of this work was to develop and integrate a mathematical, model-free analysis and a kinetic, model based analysis of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of prostate tissue, and to evaluate the clinical utility of pattern-based principle component analysis (PCA) to analyze dynamic contrast enhanced (DCE) images of the prostate, compared to the performance of model-based methods such as the three-time-points (3TP) analysis, using whole mount histology as the reference standard. **Introduction:** High resolution contrast enhanced magnetic resonance imaging has been shown to be clinically useful for staging prostate cancer.¹ The current strategies to differentiate between malignant and benign prostate tissues using DCE-MRI dataset include image subtraction and calculation of model based parameters. Naturally, recording images at high spatial and high temporal resolution, as well as high signal to noise ratio (S/N), and then analyzing them using an accurate physiological model and a robust non linear best fitting method are expected to produce the most reliable output results. However, in most clinical MRI examinations it is currently not possible to achieve these demands. In order to enhance our understanding and improve the interpretation of dynamic contrast enhanced images of the prostate we applied PCA on a clinical high spatial resolution DCE protocol performed on a 3T scanner.² **Methods:** The study was approved by the Internal Review Board of the institution and a signed Informed Consent was obtained from all patients. 14 prostate cancer patients, with prostatectomy as treatment plan, underwent a pretherapeutic MRI exam on a 3T scanner (3T Genesis Signa LX Excite, General Electric, Milwaukee, WI) using a pelvic phased-array surface coil combined with a disposable endorectal prostate coil (MRinnervu, Medrad, Pittsburgh, PA, USA). The endorectal coil was adapted from the design that has been successfully used at 1.5T. High-resolution DCE images from below the apex of the prostate to above the seminal vesicles were acquired prior, during and after a bolus injection of 0.1 mmol/kg of body weight of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) using 3D spoiled gradient echo sequence with temporal resolution of 1 min 30 sec. The imaging parameters include the following: TR/TE of 6.9/2.1 msec, flip angle of 18°, Bandwidth: 31.25, NEX: 2, FOV 14cm, matrix of 256 x 192, ST: 2.6, no phase wrap. Two precontrast and five postcontrast sequential 3D data sets were obtained, with a total acquisition time of 10 min and 27 seconds. The MR contrast agent was injected by an automated injection system (Spectris MR Injection System, Medrad, Pittsburgh, PA, USA) at a flow rate of 4 ml/s, 5-7 s before the end of the second precontrast acquisition, immediately followed by a 20ml saline flush at 4ml/s. Whole mount histopathology preparation of the excised prostate gland was performed in 14 cases. The specimen was fixed in 10% buffered formaldehyde, embedded in paraffin, sectioned (3-4 mm thickness) consecutively in planes closely paralleling the MR images and stained with Hematoxylin-eosin. Areas of carcinoma were circumscribed by one pathologist with a black dotted line, unaware of the MRI results. The whole mount histopathology slices were correlated by visual inspection to the corresponding DCE-MR images. DCE MRI data of each patient was processed by two different algorithms: PCA and 3TP. The PCA algorithm and all other application necessary for the execution were written in MATLAB™ programming environment. The seven time points of each slice were loaded into MATLAB and a region of interest (ROI), of size n voxels, for the entire prostate was determined. The input for the algorithm was a set of the n temporal vectors each of size seven. The covariance matrix was determined and its eigen values and eigen vectors were calculated. The eigen vectors were sorted in size decreasing order according to the corresponding eigen values. Two radiologists evaluated the two modalities in the 14 cases independently and assessed the accuracy of 3TP and PCA (2nd eigen vector) maps for tumor detection, location, and size in correlation with the whole mount histology. For tumor detection a 5-point scale was used (1- no tumor, 2- probably no tumor; 3- possible tumor; 4-suspicious for tumor; 5-definite tumor). For tumor location and size a similar 5-point scale was used: 1-no match; 2- little match; 3-sufficient match; 4-good match; 5- perfect match when compared to whole mount histology.

Results: The results are presented by correlation maps, which are the projection of the input vectors on the eigen vectors. The PCA decomposition produced seven correlation maps. Figure 1 shows the similarity in the three largest eigen vectors between the 14 cases. We found that high values in the 2nd and 3rd eigen vectors correlate to the suspected malignant tissue diagnosed by histopathology (Figure 2 a and b). The receiver operating characteristic (ROC) curve of the rotated 2nd eigen state displayed a high area under the curve (AUC) of 0.954, indicating the ability of this eigen-state to accurately distinguish between cancerous and benign prostate tissue. Because the PCA algorithm is performed on the covariance matrix and not on the entire data set, the execution time with our non-optimal implementation, on 10,000 input vectors was only 6 sec on a P4 3GHz PC. **3TP:** The algorithm calculates a model based calibration map for all possible values of the trans capillary transfer constants which determine the DCE-MRI time courses and selects two post contrast time points that provide optimal discrimination between benign and malignant lesions.³ The 3TP algorithm codes the signal intensity changes between the preselected time points on a per pixel basis, using color intensity and color hue as follows: The rates of enhancement in the time interval between the precontrast and 2nd point are coded by color intensity from dark to bright (slow to fast rate). The enhancement patterns during the second time interval between 2nd and 3rd points are coded with three color hues: blue, for increased signal intensity; green, for no significant change; and red, for a decrease in signal intensity. The optimal time points under the experimental conditions were precontrast set (0 minutes), postcontrast first set (45sec), and fourth set (5 min 15s). Figure 2 demonstrates a high correlation between 3TP, the second PCA eigen value and the histopathology. The two readers found the PCA maps in 13/14 cases at least as useful as the 3TP maps in tumor detection. Both readers found that 3TP and PCA showed similarly good results in accurate tumor location and prediction of tumor size, when compared to the corresponding whole mount histology, used as the reference standard. In 2/14 cases neither 3TP nor PCA maps could detect the tumor. In 2/14 cases PCA represented the tumor location and size better than 3TP. Both readers noted that in 1/14 cases 3TP maps delineated the tumor more accurately.

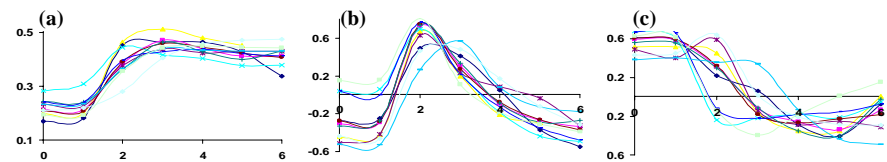
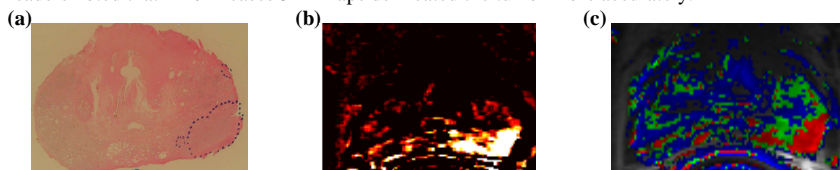


Fig 1: The results of PCA analysis for a representative slice in 14 patients. The plots show the three most significant eigen vectors (a-c) corresponding to the largest eigen values. The scales are in arbitrary units.

Fig 2: Correlation between whole mount histopathology (a), coefficient map for the 2nd eigen-vector produced by PCA (b) and the 3TP color map (c). Note that the bright white/orange area (b) and the red pattern (c) match the blue dotted cancer foci (a).



Conclusions: We have shown that the temporal patterns in DCE MRI of the prostate are a linear combination of 3 orthogonal components. The patterns were identified by PCA in 14 different cases as the three largest eigen vectors. The partition of enhancement patterns performed by PCA was similar to the partition obtained by the model base 3TP algorithm and the histopathology. While using all time points the PCA method offers a computational fast, robust, *model independent* approach for analyzing DCE MRI patterns an facilitates its interpretation. This study demonstrates the clinical utility of PCA maps of high spatial resolution DCE MRI data for accurate tumor detection and location, as well as non-invasive, accurate prediction of tumor size.

- References:**
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