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A fully automatic computer aided diagnosis system for peripheral zone prostate cancer detection using multi-parametric magnetic resonance imaging

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ABSTRACT

Multiparametric (mp)-Magnetic Resonance Imaging (MRI) is emerging as a powerful test to diagnose and stage prostate cancer (PCa). However, its interpretation is a time consuming and complex feat requiring dedicated radiologists. Computer-aided diagnosis (CAD) tools could allow better integration of data deriving from the different MRI sequences in order to obtain accurate, reproducible, non-operator dependent information useful to identify and stage PCa. In this paper, we present a fully automatic CAD system conceived as a 2-stage process. First, a malignancy probability map for all voxels within the prostate is created. Then, a candidate segmentation step is performed to highlight suspected areas, thus evaluating both the sensitivity and the number of false positive (FP) regions detected by the system. Training and testing of the CAD scheme is performed using whole-mount histological sections as the reference standard. On a cohort of 56 patients (i.e. 65 lesions) the area under the ROC curve obtained during the voxel-wise step was 0.91, while, in the second step, a per-patient sensitivity of 97% was reached, with a median number of FP equal to 3 in the whole prostate. The system here proposed could be potentially used as first or second reader to manage patients suspected to have PCa, thus reducing both the radiologist's reporting time and the inter-reader variability. As an innovative setup, it could also be used to help the radiologist in setting the MRI-guided biopsy target.

1. Introduction

Multiparametric magnetic resonance imaging (mp-MRI) combines morphological and functional information and is being increasingly used to detect cancer. One of the most promising applications of mp-MRI is to detect prostate cancer (PCa) [1–3]. Current indications of mp-MRI include patients with rising levels of prostatic-specific-antigen (PSA) after one or more negative transrectal ultrasound guided (TRUS) biopsies [4,5]. One good reason why mp-MRI has not yet progressed to becoming a front-line imaging modality to detect PCa is because it is a labour-intensive examination and has a steep learning curve. Indeed, interpretation requires experienced radiologists capable of analysing data extracted from the different MR sequences [5,6].

Computer aided detection (CAD) systems have the potential to support the radiologist by indicating suspicious regions and reducing oversight and perception errors [7]. In addition, some CAD applications have been shown to be time efficient [8]; however, this may be accomplished only if minimal or no human interaction is required in post-processing.

The implementation of a fully automatic CAD system is not a trivial problem. Chan et al. first implemented in 2003 a CAD system for the diagnosis of peripheral zone (PZ) PCa, using a support vector machine (SVM) classifier [9]. Vos et al. [6] developed in 2012 a CAD scheme using multiple sequential steps, including initial blob detection on apparent diffusion coefficient (ADC) maps followed by a local feature analysis by a supervised classifier. Similarly, Niaf et al. [10] used a SVM classifier combined with a *t*-test feature-selection method, and achieved an area under the ROC curve (AUROC) equal to 0.82. Finally, Litjens et al. [5] included different stages in their CAD system, investigating a novel voxel classification step in combination with a candidate classification stage.

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None of the described studies has adopted a fully automatic registration step to align both the Dynamic Contrast Enhanced (DCE-MR) and the Diffusion Weighted (DW) to the T2-weighted (T2w) image. In this study, we present a fully automatic CAD system for PCa detection, which seeks to overcome the limitation of previous related works. Training and testing of the CAD scheme is performed using whole-mount histological sections as the reference standard.

2. Materials and methods

2.1. Patients

This was a single institution study. We enrolled all individuals that complied with the following inclusion criteria: (a) biopsy-proven prostate adenocarcinoma, (b) mp-MRI examination between April 2010 and November 2012, including axial T2w, DW, and DCE-MR sequences, (c) radical prostatectomy (RP) within 3 months of MRI, and (d) a clinically significant PZ lesion (tumour volume $\geq$0.5 ml) [11] at the whole-mount histopathologic analysis. The local Ethics Committee approved the study and participants in the study signed informed consent forms. This study was in accordance with the Helsinki Declaration.

2.2. MR image acquisition

Images were acquired with a 1.5 T scanner (Signa Excite HD, GE Healthcare, Milwaukee, Wisconsin, USA) using a four-channel phased-array coil combined with an endorectal coil (Medrad, Indianola, Pa). Axial T2w images were obtained using the following protocol: slice thickness, 3 mm; field of view (FOV), 16 × 16 cm; NEX, 2; acquisition matrix, 384 × 288; reconstruction matrix, 512 × 512; TR/TE, 3020/85 ms. DW imaging was obtained using axial Echo-Planar Imaging sequences as follows: slice thickness, 3 mm; FOV, 16 × 16 cm; acquisition matrix, 128 × 128; reconstruction matrix, 256 × 256; NEX, 6; TR/TE, 7000/101 ms; *b*-values, 0 and 1000 s/mm^2. Finally, a 13 s time resolution DCE study was performed, with an axial 3D Spoiled Gradient echo (SPGR) sequence using the following parameters: TR/TE/FA, 3.6 ms/1.3 ms/20°; FOV, 20 × 20 cm; slice thickness, 3 mm; acquisition matrix, 224 × 192; reconstruction matrix, 512 × 512. Scanning started simultaneously with the intravenous injection of 0.1 mmol/kg gadobutrol (Gadovist, Bayer Schering, Berlin, Germany) through a peripheral line at 0.7 ml/s, using a power injector (Medrad Spectris, Maastricht, The Netherlands), followed by infusion of 20 cm^3 normal saline at same rate. Twenty-six contrast-enhanced frames were obtained. The average time to complete the whole MR exam, including two additional T2w scans in the sagittal and coronal plane, was 40 min. Overall imaging parameters satisfied the minimal scanning requirements [4].

2.3. Reference standard and MR correlation

The prostate specimen was step-sectioned at 3 mm intervals perpendicular to the long axis (apical-basal) of the gland [12]. This confidently reproduces the inclination of axial T2w images, which were acquired perpendicular to the rear gland surface. The bases and the apexes were cut parasagittally. Five μm sections were then obtained and coloured with hematoxylin eosin. The pathologist (E.B., with 24 years of experience in pathology, 20 attending uropathology) outlined each clinically significant peripheral tumour on microscopic slices and assigned a pathological Gleason Score (pGS). The radiologist (F.R., with an experience of more than 500 prostate mp-MRI studies interpreted per year for 6 years) in consensus with the pathologist, established the reference standard for PCa on T2w images drawing freehand regions of interest (ROIs) on cancer foci, following the outlines drawn by the pathologist on digital images of the pathologic slices. When pathological microslices and axial T2w images were not perfectly overlapped, usually due to modified prostate shape soaked by formaldehyde, the radiologist and the pathologist established the locations of tumours with respect to identifiable anatomic landmarks (e.g., adenoma nodule, urethra, ejaculatory ducts, and benign prostatic hyperplasia). If a lesion extended into more than one histopathologic slice, a ROI was drawn on each corresponding MR slice. For each patient a ROI, with extension similar to the tumoural region, was also drawn on normal gland located in the contralateral PZ.

2.4. CAD pipeline

The pipeline of the CAD system is shown in Fig. 1; it is conceived as a 2-stage process. First, a parametric colour-coded map of the prostate gland is created; colours are assigned to the map based on the probability of each voxel to be cancerous (Fig. 1A). Then, a candidate segmentation step is performed to highlight suspected areas (Fig. 1B). Different fully automatic steps, thoroughly described in the following subsections, compose each of these stages. All methods are implemented using C++ and the ITK libraries [13].

2.4.1. Image registration

Image registration has been described in detail elsewhere [14]. Registration is an important step as it allows to correctly align different types of images so that features, derived from all the MR sequences and referring to the same pixel or group of pixels, may be compared and studied. Before applying the registration methods, both the DCE volumes and the DW images have been upsampled to the T2w image resolution, and the DCE volumes were also automatically cropped to match the same FOV of the T2w image. The algorithm first aligns DW to the T2w images, by applying a non-rigid registration step. In particular, the deformation field is modelled as a linear decay field along the vertical direction (1), assuming that the pixel shifts caused by magnetic field inhomogeneities occur particularly in the phase encode direction and decrease linearly with distance from the coil (1).

$$T(y) = \begin{cases} d_l - k * y & 0 < y < \dfrac{d_i}{k} \\ 0 & y > \dfrac{d_i}{k} \end{cases} \quad (1)$$

Moreover, the DCE images are aligned to the T2w sequence using a multi-resolution rigid registration algorithm. In this case, the registration is solved as an optimization problem with the goal of finding the optimal transformation T:$(x,y,z) \rightarrow (x',y',z')$ which maps any point in the moving DCE dynamic image sequence $I(x,y,z,t)$ at time t into its corresponding point in the reference image $I(x,y,z,t0)$, i.e., the T2w. The mutual information, which is a measure of statistical dependency between two datasets, has been used as similarity metric and the regular step gradient descent algorithm has been used as optimizer [14].

2.4.2. Prostate segmentation

The segmentation of the prostate is of key importance to reduce the computational burden of the CAD system. In our method we first automatically identify on each slice a rectangular region of fixed size (i.e., width = 7 cm, height = 6 cm). The rectangle is automatically generated in such a way that its posterior border is in contact with the anterior profile of the coil, which is segmented using the Hough transform on the T2w image. It may confidently enclose both a normal (size = 4 × 2 × 3 cm) and an enlarged prostate [15]. Then, we extract the ADC map on this rectangular region and we apply, on the selected region, the multi-level Otsu threshold