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FULL PAPER

Symmetry based prostate cancer detection

^{1,2}L YANG, PhD, ^{1,3}Y XIE, MS, ⁴B LI, PhD, ¹M XIE, BE, ⁵X WANG, MD and ^{3,4}J ZHANG, PhD

¹College of Electronic Engineering, Chengdu University of Information Technology, Chengdu, Sichuan, China

²School of Electronic Engineering, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

³Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China

⁴College of Engineering, Peking University, Beijing, China

⁵Department of Radiology, Peking University First Hospital, Beijing, China

Address correspondence to: Professor Xiaoying Wang

E-mail: cjr.wangxiaoying@vip.163.com

Objective: To retrospectively assess the value of left and right half symmetry analysis in prostate T_2 weighted images (T2WI) for improving prostate cancer (PCa) screening.

Methods: T2WI and other data of a total of 66 males were collected; the control group and cancer group had 33 patients each. Thresholding geometric active contours algorithm was used for prostate region segmentation, and the measure of local reflectional symmetry algorithm was applied to extract the longitudinal symmetry axes. After that, cross-correlation coefficients (CCs) of the left and right halves of each prostate were obtained.

Results: Data analysis showed that the mean and variance of the value of the left and right half CCs of prostate T2WI

in the cancer group and control group were 0.73 ± 0.05 and 0.82 ± 0.06 , respectively. The area under the receiver operating characteristic curve was 0.87, and the specificity and the sensitivity were 91% and 70%, respectively. The $p < 0.001$ indicated that the value of CCs of the prostates between the two groups was significantly different.

Conclusion: The symmetry in T2WI is a potential useful index for PCa screening and has a potential value for PCa detection and localizations of tumours for biopsy.

Advances in knowledge: Texture bilateral symmetry of prostate T2WI is employed to screen the suspected prostate tumour.

Prostate cancer (PCa) is the second most common cancer among males worldwide¹ and the most common cancer among Western males.^{2,3} With rapid increase, especially, in old people, the number of total sufferers is expected to increase so that by 2020, it is only exceeded by lung cancer.^{4–7} PCa was the sixth most frequently diagnosed cancer among males during 2008 in the Asia-Pacific region, behind cancers of the lung, stomach, liver, colorectum and oesophagus. This pattern was mainly driven by Eastern Asia, and in particular China, which represents about 62% of the region's male population.⁸ More than that, PCa is now becoming an emerging health priority in East Asia. Because East Asia remains the world's most populous region, the number of individuals with PCa will increase substantially in the coming decades.⁹

Currently, PCa screening relies on digital rectal examinations (DREs) and serum prostate specific antigen (PSA) levels. But PCa diagnosis is based on histological tissue analysis, which is most often obtained via needle biopsy, guided by transrectal ultrasound (TRUS). However, it has been reported that its accuracy is only 20–25% in patients with PSA levels between 4 and 10 g ml^{-1} owing to the inevitable inaccurate positioning

during TRUS, and often leads to the failure to detect cancer.^{10,11} Additionally, repetitive biopsies will not only increase the suffering of patients but also lead to increased rate of complications. For these reasons, image modalities and suspicious lesion identification *via* computer-aided diagnosis (CAD) methods are expected to provide more accurate detection and localization of prostate tumours. MRI is commonly employed in some areas to assist in the diagnosis of PCa and provide locations of suspicious tumours before biopsy, and accurate CAD methods are urgently needed.^{11–18}

In recent years, many efforts have been made to evaluate MR-based suspected prostate lesions. Firstly, Dickinson et al¹⁹ developed a standardized reporting scheme that may be widely adopted and validated to ensure comparability of research outputs and optimal clinical practice. Secondly, dynamic contrast-enhanced MRI (DCE-MRI) has been extensively used for the diagnosis of PCa. DCE-MRI is an important imaging technique because it can detect angiogenesis and vasculogenesis of tumours. Jackson et al¹² calculated the accuracy of DCE-MRI for cancer detection by a pixel-by-pixel correlation of quantitative DCE-MRI parameter maps and pathology, and the results showed

a significant difference between the benign peripheral zone and tumour for the parameters K^{trans} , v_e and k_{ep} . Based on DCE-MRI, Puech et al¹⁵ provided a standardized cancer suspicion score for suspicious foci based on the median wash-in and wash-out values of peripheral zone cancer, peripheral zone benign, transitional zone cancer and transitional zone benign to provide useful data for an unbiased and reproducible assessment of hypervascularized prostatic areas in routine practice.

T_2 weighted images (T2WI) play a crucial role in clinical practice, by distinguishing between normal and abnormal foci in prostate zonal anatomy and periprostatic structures.²⁰ With fast spin-echo techniques, T2WI was adopted by Sommer et al²¹ to detect some early stages of PCa, such as pelvic lymph nodes or pelvic bone metastases,^{22–24} and it is already routinely used in prostate lesion identification.

Some recent studies have provided clinical assessments utilizing the prostate T2WI features. Madabhushi et al¹⁰ firstly presented a CAD system for detecting PCa from high-resolution MRI studies, which used three-dimensional (3D) texture operators to capture a wider range of variation in appearance, size, orientation and anisotropy of the cancer. Lv et al¹⁶ offer a robust MR-based indicator to distinguish prostate tumours from normal tissue with a fractal analysis to extract the features of the prostate texture and intensity distribution on T2WI as indices in the differential diagnosis of PCa. Local texture patterns in T2WI were considered in previous computer-aided approaches for automatic prostate lesion detection, but the morphological characteristics, such as symmetry, which is easily observed in prostate T2WI, were ignored. Bilateral symmetry appears commonly in nature, including many organs in our bodies such as the brain, bones, skin and prostate. As for a developing lesion, asymmetry gradually appears with symmetry breaking down in tissue because of differentiation of perfusion, blood supply and metabolism beyond normal tissues.²⁵ Radiologists have reported that symmetry in prostate MRI can be important to detect PCa.²⁶ Litjens et al²⁷ also investigated a fully automated computer-aided detection system for the diagnosis of PCa that includes feature of symmetry, local contrast and shape. In this study, texture bilateral symmetry of prostate T2WI is employed to screen the suspected prostate tumour, which is a potential useful index to help identify and localize the lesions or tumours in patients who undergo PCa screening.

METHODS AND MATERIALS

Database

Data collections were approved by the institutional review board of Peking University First Hospital, and informed consent was obtained from all participants. Data from a total of 66 patients were collected for this investigation. The data collected from each patient included DRE findings, pathological results of ultrasound-guided biopsy, PSA level and T2WI.

The mean patient age was 72 years in the control group consisting of 33 patients (age range, 51–80 years) whose previous diagnosis indicated no histological abnormality. The mean of

the serum PSA level is 10.3 ng ml^{-1} , ranging from 0.59 to 31.58 ng ml^{-1} .

The mean patient age is 72 years in the PCa group consisting of 33 patients (age range, 56–85 years) whose previous biopsies were with a Gleason score of 7 or higher. The serum PSA level ranged from 4.03 to 39.00 ng ml^{-1} with a mean of 14.21 ng ml^{-1} .

All the 66 patients were suspected of PCa on the basis of serum PSA values, DRE results or transrectal ultrasound results. The patients in the control group were followed for at least 16 months and some up to 4 years, and routinely underwent repeated prostate biopsy at 12- to 24-month intervals, and their biopsies had negative pathological results, even though they had relatively high PSA values.

MRI

MRI of transverse T2WI of the prostate and seminal vesicles were performed by using a 1.5-T whole-body MR imager (Signa®; GE Medical Systems, Milwaukee, WI). Using a body coil, patients were imaged in a supine position, using a pelvic phased-array coil (GE Medical Systems) for getting signal reception with the following parameters. A fast spin-echo sequence was employed: echo train length, 12–16; field of view, 26 cm; matrix, 320×256 pixels; section thickness, 3 mm; repetition time/echo time, 3800 ms/139 ms; intersection gap, 0 mm; field of view, 26 cm; matrix, 320×256 pixels; number of excitations, four. The total MR acquisition time was about 3 min generally.

Bilateral symmetry analysis

The proposed computer-assisted approach is divided into three steps: prostate region segmentation based on threshold active contours (TAC), symmetry axis estimation and finally similarity evaluation of prostate left (L)–right (R) half part. The diagram of processing is presented in Figure 1.

Firstly, the prostate on the transversal T2WI was segmented with the proposed localized level-set model for improving segmentation accuracy of the whole prostate zone. Subsequently,

Figure 1. Flow diagram of processing to get similar cross-correlation estimation between the right and left halves of the prostate. MLRS, measured local reflectional symmetry; T2WI, T_2 weighted images; TAC, threshold active contours.

the measured local reflectional symmetry (MLRS) was employed to explore the symmetry axis of the prostate zone. After evaluating the angle between the orthogonal symmetry axis and image axis, the rotation correction of the prostate images was carried out accordingly. Then, with the estimated longitudinal symmetry axis, prostate zones could be separated into two parts: L and R sides. And mirrored result of L, namely L', could be obtained easily by a mirror operation about the longitudinal symmetry axis. Finally, the maximum cross-correlation between L and L' was evaluated by classical image correlation.

More details are described below, and each of the steps are described in more detail in the corresponding subsections.

Prostate zone segmentation

In order to extract the prostate region from a given T2WI, the TAC technique, which combines the level-set-based geometric active contour approach and the classical thresholding technique was used.

The energy function used in the TAC is represented by:^{28–30}

$$E_{\text{image}}(\phi, I) = \|H(\phi) - G(C)\|^2 = \int_{\Omega} \{H[\phi(x)] - G[\tau, I(x)]\} dx \quad (1)$$

The energy E_{image} is the L^2 distance between the current segmentation $H(\phi)$ obtained from the curve C and the implied segmentation G obtained from thresholding the image I . $H: R \rightarrow \{0, 1\}$ is the Heaviside step function:

$$H_{\varepsilon}(x) \begin{cases} = 1 & \text{if } x > \varepsilon \\ = 0 & \text{if } x < -\varepsilon \\ = \frac{1}{2} \left[1 + \frac{x}{\varepsilon} + \frac{1}{\pi} \sin\left(\frac{\pi x}{\varepsilon}\right) \right] & \text{otherwise} \end{cases} \quad (2)$$

The gradient $\nabla_{\phi} E_{\text{image}}$ can be computed using calculus of variations [both $H(\phi)$ and G depend on ϕ]:

$$\nabla_{\phi} E_{\text{image}} = 2\delta(\phi)[H(\phi) - G] + 2(\beta_1 \times \nabla_{\phi} I_1 - \beta_2 \times \nabla_{\phi} I_2) \quad (3)$$

where the expressions of $\beta_1 \in R$ and $\beta_2 \in R$ are:

$$\beta_1 = \int_{\Omega} \delta_{\varepsilon_1}[I(x) - I_1] \{H[\phi(x)] - G(x)\} dx \quad (4)$$

$$\beta_2 = \int_{\Omega} \delta_{\varepsilon_2}[I(x) - I_2] \{H[\phi(x)] - G(x)\} dx \quad (5)$$

A typical segmental result based on TAC is shown in Figure 2b,g.

Symmetry axis selection

To evaluate the symmetry of a given prostate region, we used the MLRS, an approach that was proposed by Kiryati and Gofman,³¹ to determine the symmetrical axis of the prostate region.

The framework of MLRS is to transform the symmetry detection problem into a global optimization problem, to find the global maximum of a complicated multimodal function parameterized by the location of the centre of the supporting region, its size and the orientation of the symmetry axis.³¹

Figure 2. (a–e) A normal prostate processed by the scheme shown in Figure 1 (f–j) referred to a cancerous one. (a, f) The prostate T_2 weighted images. (b, g) The prostate zones extracted from (a, f) using threshold active contours method, the dashed lines represent the symmetry axes of the prostates obtained by measured local reflectional symmetry. (c, h) The corrected prostate regions by rotation according to the symmetry axes shown in (b, g). (d, i) The left-half prostate regions. (e, j) The mirrored right-half prostate regions.

Accordingly, assuming $f(x, y)$ is a two-dimensional (2D) real function that can be considered to be zero everywhere except within a circle of radius L centered at the origin, the 2D symmetry axis measure can be expressed as follows:

$$S_{\theta}(f) = \frac{\iint f(t, s)f(t, -s)dsdt}{\iint f(t, s)dsdt} + \frac{1}{2}s \quad (6)$$

$$\begin{cases} t = x \cos(\theta) + y \sin(\theta) \\ s = y \cos(\theta) - x \sin(\theta) \end{cases} \quad (7)$$

where S_{θ} is the symmetry measurement when the longitudinal and transverse axes rotate θ angle, and t, s are the new orthogonal axes. In the article, it assumes that the origin point locates on the centre of an image. When S_{θ} reaches a maximum, the symmetry axis angle of departure from the y -axis is obtained. The result is shown in Figure 2b,g, in which the dashed lines represent the symmetry axes. The image was rotated until the symmetry axes of the prostates obtained by MLRS were perpendicular to the horizontal direction.

By rotating Figure 2b,g with the angle θ , the corrected image is obtained, which is demonstrated in Figure 2c,h.

Symmetry evaluation

After angle correction based on the extracted symmetry axis, the prostate zone is divided into the left and right sides. Then, the left half prostate mirrored about the symmetry axis, and is shown in Figure 2e,j. Finally, the cross-correlation coefficients (CCs) was used to evaluate the similarity between left and mirrored right regions, which is given by Lewis.³²

Statistical analysis

To determine the statistical significance of differences in CCs between case and control groups, we consider the prostate as the unit of statistical analysis, for example, in our data, each group has 33 CCs. And then, the mean and the standard deviations (SDs) of CCs can be calculated for each group. The significance of the difference is assessed by using t -tests based on two groups of CCs with 95% confidence intervals (CIs). $p < 0.05$ was considered to indicate a significant difference in our experiments.

The analysis of receiver operating characteristic (ROC) curves is utilized for appraising the assortment properties of the cross-correlation, with biopsy findings as the golden standard. The area under the ROC curve (AUC) was applied as a parameter to appraise the immanent distinguishing ability of cross-correlation between cases and controls.

RESULTS

The CCs of 33 prostate zones from the PCa group were compared with those of 33 prostate zones from the control group. The means and SDs of the CCs for the cancer group and control group were 0.73 ± 0.05 and 0.82 ± 0.06 , respectively. This reveals that the cross-correlation of the cancerous prostate zones have lower means than that of the controls. Figure 3a explains

the symmetric features by means of box plots to present the statistical distribution of the CCs, which illustrates the degree of differences of bilateral modality and intensity components between the prostates from the two groups. The t -test result indicates that the group difference of cross-correlation is statistically significant ($p < 0.001$).

Figure 3. (a) Box-plots of statistical distributions for cross-correlation coefficients (CCs), in the prostate zones of control and prostate cancer groups; (b) the receiver operating characteristic (ROC) curves obtained from CCs in the classification of the control group and the cancer group prostates (66 prostates). The area under the ROC curve value is 0.87, and the sensitivity and specificity are 91% and 70%, respectively.

(a)

(b)

The ROC curve is shown in Figure 3b, which yielded an AUC value of 0.87 for cross-correlation. With the cut-offs of sensitivity = 91% and specificity = 70%, the estimated standard errors of the AUC values was 0.05. At 95% confidence level, the CIs is 0.78–0.95.

DISCUSSION

In this work, we attempt to utilize the bilateral symmetry to screen PCa by MR T2WIs. Our study demonstrated that the method based on prostate symmetric analysis is feasible to differentiate quantitatively between normal and cancerous prostates. The method used whole morphology symmetric cross-correlation to characterize the T2WI associated with PCa. Our results illuminated significant difference between cancer and normal groups, and the cancerous prostate has lower bilateral cross-correlation than normal ones. There are several potential uses for our results. Firstly, the symmetric feature could be used as an independent index in automated computer-aided detection systems. Automatic systems to detect PCa could reduce the workload of doctors so that they do not have to read large numbers of 3D images and make the radiologist more sensitive to the suspected region. Secondly, the segmentation result of our method could be helpful in automatic medical image analysis. Precise and automatic segmentation is important for medical image analysis, but researchers always intervene with the automatic process by manually isolating the interesting region owing to a lack of effective automatic segmentation. Thirdly, the result may contribute to screening of PCa using MRI. More accurate detection of MRI could improve the sensitivity and specificity over PSA and TRUS that are the first choice in clinical practice.

For most normal prostate zones, both the external shape and the internal texture appear highly symmetrical, and a symmetrical axis exists in the middle of the central gland in T2WI. However, owing to the existence of pathological tissue in prostate tumour, there exists different extents of asymmetry in texture caused by capsular thickening and local uplift, and even prostate rectal angle will disappear for the malignant lesions, both sides of the neuro-vascular bundle and the surrounding venous plexus are no longer symmetrical. Based on these pathological characteristics, if cancer foci break through the capsule, morphology asymmetry inevitably exists. As the whole texture symmetry is broken by tumours, the bilateral intensity distribution symmetry also is gradually ended. It has been shown that external contours and entire morphologies of the prostate that were assessed by DRE appear not to be independent risk factors for detecting PCa.³³ However, the characteristic of asymmetry in our study is the internal organizational structure of the prostate that relates to the texture asymmetry, which differs from the mentioned research of Hansen et al.³² The findings of Hansen et al are based on uneven growth between the lateral lobes of the prostate that were assessed by DRE.

Using these characteristics, we can quantitatively analyse the degree of symmetry between the left and right sides of the prostates by cross-correlation in T2WI, which proves to be an effective means in screening PCa.

Our study illustrated the symmetry difference of intensity between normal and cancerous prostate. As shown in Figure 4, the colour

map visualizes the difference of the intensity distribution between the left and right halves. The intensity difference between the left and right halves of a normal prostate is far lower than those of a cancerous prostate, and the healthy prostate has a more uniform distribution of image pixel intensity. Furthermore, the area in the right peripheral zone in Figure 2f has identified prostate tumours, and at the same position in Figure 4b, it contains areas of considerably higher pixel intensity. The correlation indicates that

Figure 4. Corresponding to Figure 2c,h, two colour maps (a, b) of bilateral intensity difference. (a) The cross-correlation coefficients (CCs) of the normal prostate T_2 weighted images (T2WI) is 0.92. (b) The CCs of the cancerous prostate T2WI is 0.78. It indicates that the smaller the CCs, the greater the difference in their bilateral gray.

highlighting areas of asymmetry in the colour map has the potential for tagging suspicious or diseased tissue. The normal peripheral zone is very bilaterally symmetrical in T2WI leading the pixel values in the intensity difference map are low, which was rendered as black in Figure 4a. Once tumours exist on either side of the peripheral zone, symmetry will be broken down and be shown as light gray areas in the T2WI. The colour map has the potential to assist the diagnosis of cancerous peripheral zones and possibly locate lesions. It has been reported that approximately 65–75% of PCa cases occur in the peripheral zone,^{34,35} the colour map may be helpful for diagnosing PCa.

In our study, it is necessary to isolate the prostate region from a given T2WI. Precise segmentation is crucial to calculate accurate CCs. By TAC combining intensity threshold and geometric active contours, the curve can naturally evolve with topological changes, such as splitting and merging, which can produce accurate segmentation results. The TAC could be used as a contour model for shape description and is based on dynamically computing the best threshold image as a function of the segmenting curve at each step of the contour evolution. Practically, it is able to deal with complicated image segmentation, which is suitable for medical image segmentation.

Among some normal prostate T2WI, the longitudinal symmetry axes are not along with y -axis, resulting in an inclined image matrix (Figure 2b,g), this needlessly complicates the calculation of the cross-correlation. Therefore, we need to extract the symmetry axis of each prostate image and rotate whole image to make the symmetry axis line-up with the y -axis, which produces a regular image matrix and makes the calculation easy and efficient. In this article, the MLRS algorithm was employed to explore the symmetry axis of the prostate zone, and set the angle precision to within 0.1° to yield more accurate results. Bicubic interpolation was adopted to reduce the gray discontinuousness for rotation so that the computation of CCs was more precise.

There are also some limitations in our methods. The present study used whole morphology symmetry of prostates and only compared normal prostates with cancerous prostates. Patients with benign pathology were not included in this study. Benign lesions, such as prostatitis, haemorrhage and calcification, exist in many prostate glands, completely destroying the left–right symmetry while not being cancerous. Therefore, it is difficult

to discriminate benign lesions from cancerous lesions in a prostate by means of morphology analysis. Utilizing intensity symmetry property of prostate in T2WI, however, can be helpful to resolve the situation. Thus, the next step is to verify whether intensity symmetry index can differentiate between normal tissue and lesions that are not present near the outer edge of the prostate.

We used the TAC method of image segmentation, which was applied to get the whole prostate zone. Although it improves the segmentation results while avoiding the deficiencies of other models, which use global information or edge information only, we face problems when it handles where the prostate intersects the peripheral area. If the initial manually selected contour contains some other tissues, the final iterative result will deviate from the actual prostate contour, and the degree of deviation depends on the proportion of other tissues. So for accurate results, the initial manual contour selection must include as little other tissue as possible. Furthermore, for some rare cases, the segmentation algorithm fails to get the correct boundary of the prostate owing to the severe adhesion between the prostate and surrounding tissue. Although we did not compare the result of the segmentation algorithm with that of artificial segmentation, the segmentation results were confirmed by doctors to ensure that the regions of interest were completely isolated. In the future work, we will study whether the more precise segmentation could improve the performance of our scheme.

The present study is based on the symmetrical feature of prostates. However, some males without PCa have relatively asymmetrical prostate morphology, so this method is only effective for detecting asymmetry, and thus cancer, in normally symmetrical prostates.

CONCLUSION

In conclusion, cross-correlation shows statistically significant differences between cancerous and control group prostates using T2WI. Cancerous tissue tends to be less bilaterally symmetrical, and thus the CCs intensity distribution of cancer cells is less uniform than that of normal tissue, which is consistent with clinical experiences. The symmetric feature provides helpful MR-based quantitative indices for improving PCa screening and could provide useful information to identify and localize tumours in the future.

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