Purpose: Multiparametric MRI (mpMRI) has shown promise in the detection and localization of prostate cancer foci. Although techniques have been previously introduced to delineate lesions from mpMRI, these techniques were evaluated in datasets with T2 maps available. The generation of T2 map is not included in the clinical prostate mpMRI consensus guidelines; the acquisition of which requires repeated T2-weighted (T2W) scans and would significantly lengthen the scan time currently required for the clinically recommended acquisition protocol, which includes T2W, diffusion-weighted (DW), and dynamic contrast-enhanced (DCE) imaging. The goal of this study is to develop and evaluate an algorithm that provides pixel-accurate lesion delineation from images acquired based on the clinical protocol.

Methods: Twenty-five pixel-based features were extracted from the T2-weighted (T2W), apparent diffusion coefficient (ADC), and dynamic contrast-enhanced (DCE) images. The pixel-wise classification was performed on the reduced space generated by locality alignment discriminant analysis (LADA), a version of linear discriminant analysis (LDA) localized to patches in the feature space. Postprocessing procedures, including the removal of isolated points identified and filling of holes inside detected regions, were performed to improve delineation accuracy. The segmentation result was evaluated against the lesions manually delineated by four expert observers according to the Prostate Imaging-Reporting and Data System (PI-RADS) detection guideline.

Results: The LADA-based classifier (60 ± 11%) achieved a higher sensitivity than the LDA-based classifier (51 ± 10%), thereby demonstrating, for the first time, that higher classification performance was attained on the reduced space generated by LADA than by LDA. Further sensitivity improvement (75 ± 14%) was obtained after postprocessing, approaching the sensitivities attained by previous mpMRI lesion delineation studies in which nonclinical T2 maps were available.
1. INTRODUCTION

Prostate cancer is one of the most commonly diagnosed cancers and a leading cause of mortality worldwide. Prostate cancer is the most common nonskin cancer in North America,\textsuperscript{1,2} In Hong Kong, prostate cancer accounted for 11.3\% of all new cancer cases in male and was the third most common cancer in men in 2014.\textsuperscript{3} The first-line screening tests include digital rectal examination (DRE) and serum prostate-specific antigen (PSA) tests. If either result is suspicious for cancer, transrectal ultrasound-guided (TRUS-guided) prostate biopsy is performed to evaluate the presence of cancerous lesions. Although the prostate gland can be delineated from TRUS images,\textsuperscript{4,5} cancer lesions cannot usually be seen by ultrasound and locations where biopsy is performed are determined by protocols established based on previous clinical observations.\textsuperscript{6} Due to the inability of TRUS in targeting lesions, up to 35\% of the lesions are missed in the first TRUS-guided biopsy.\textsuperscript{7} Repeated biopsies are needed, leading to increased emotional stress for patients. Thus, sensitive image-based tools allowing precise lesion localization are required to increase the yield of the biopsy procedure. In addition, the advent of prostate cancer focal therapy has provided options for localized tumors to be treated with a lower risk of morbidity in the urinary and reproductive systems. Delivering these therapies while minimizing collateral damages to surrounding healthy tissues requires accurate lesion localization.

MRI has been used to detect prostate cancer for over three decades.\textsuperscript{8} Early diagnosis techniques focused on imaging the morphological or anatomical irregularities based on the signal contrast displayed in T2W images. Although T2W images have high tissue contrast and high spatial resolution for visualization of zonal anatomy and tumor, it has limited sensitivity and specificity for prostate cancer detection. Some lesions are isointense to neighbouring healthy tissues, resulting in the relatively poor sensitivity. The specificity is also limited because benign abnormalities, such as postbiopsy hemorrhage and prostatitis, may mimic lesions in T2W images. Multiparametric MRI (mpMRI) combines anatomic T2W and functional techniques, including diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI to enhance detection and localization accuracy. Lesions are associated with reduced water diffusion due to higher cellular density. The restricted diffusion can be measured by DWI. The apparent diffusion coefficients (ADC) characterizing the amount of diffusion calculated from multiple DW images are typically displayed as a parametric map to facilitate assessment. DCE MRI depicts the vascularity of tissues by following the temporal signal variations after injection of a contrast agent. Lesions can be detected by DCE MRI as they are associated with increased vascularity, which leads to early hyperenhancement and rapid washout of the contrast agent.

Although studies in prostate cancer detection and localization research based on mpMRI have been performed,\textsuperscript{9–17} most studies focus on the localization of lesions in coarse regions instead of tumor delineation. The prostate was divided into 6–30 regions in these studies. Radiologists then visually identified regions on which lesions lie by reviewing a subset or all of T2W, ADC and DCE MR images. Studies have suggested that when combined with T2W, DCE MRI increases the sensitivity of lesion detection,\textsuperscript{14,16} whereas DWI improves specificity,\textsuperscript{9,11,15} with optimal localization accuracy obtained when all three sequences were used.\textsuperscript{10,12,14,17} Since these studies applied different schemes to define prostate regions, there is a large variation in the results obtained across studies; for example, sensitivity and specificity of T2W images were reported to range from 54 to 91\% and 27 to 91\%, respectively.\textsuperscript{9,10,18} Another limitation of these studies is that they all required radiologists to identify lesions by working through many transverse MR images, and manual identification is time-consuming and subject to observer variability. The lack of standardization in mpMRI acquisition protocol as well as in interpreting and reporting mpMRI results further lead to the discrepancy in the conclusions made by different investigations.\textsuperscript{19} For this reason, consensus guidelines on interpreting mpMRI have been developed by experts from the European Society of Urogenital Radiology (ESUR) and the American College of Radiology (ACR).\textsuperscript{20,21} However, as the mpMRI assessment was performed by human observers in previous studies, a substantial interobserver variability still exists.\textsuperscript{22,23,24} As the consensus guidelines are expected to be more commonly adopted in clinical practice, a major motivation of this study is to develop an automated technique that can delineate lesions from the consensus acquisition protocol reproducibly after trained by a number of expert observers.

Although pixel-based prostate cancer classification techniques based on mpMRI have been previously described,\textsuperscript{25–29} these techniques were not designed to analyze the MR images obtained in standard protocols described in the consensus guidelines. In particular, quantitative T2 maps were available for the pixel-based lesion localization algorithms reported in Refs. [25–29]. Although T2 maps are superior to the T2W images in that T2 maps are not confined by acquisition parameters, such as TR, and the
variation in the signal intensity as a function of the distance from the endorectal coil, computation of the T2 map required the acquisition of the T2W fast spin-echo images for ten echo times. The significant lengthening of the scanning time required for the generation of T2 maps is ill-afforded in clinical practice considering that standard protocols described in the consensus guidelines, which include T2W, ADC, and DCE imaging, but not T2 maps, have already taken 30–45 min.\textsuperscript{20}

Lesion delineation from mpMRI requires the classification of each pixel to either a part of a cancer lesion or the background. Classification is commonly achieved by finding the nearest neighbour in the feature space. Euclidean distance, however, becomes less meaningful in a high-dimensional feature space as the Euclidean distance to a point’s furthest neighbour approaches that to its closest neighbour when the dimension increases to as few as 15 as shown in Beyer et al.\textsuperscript{30} The poor contrast in distances to different data points would render the use of nearest neighbour classifier questionable. For this reason, there was a need to reduce the dimensionality of the feature space before a nearest neighbour classifier was applied in this study as more than 20 features were extracted for each pixel. Linear discriminant analysis (LDA) is among the most widely used dimensionality reduction approaches in which a projection matrix is found to maximize the trace of the between-class scatter matrix and minimize the trace of the within-class scatter matrix simultaneously. A widely used formulation of LDA is to maximize the trace ratio of the between- and within-class scatter matrices. However, distribution of data points in different regions of the feature space may be highly inhomogeneous; in this situation, minimization of trace ratio of the between- and within-class scatter matrices constructed from the entire dataset compromises the discrimination performance of LDA. To address this issue, Tang et al.\textsuperscript{31} developed the locality alignment discriminant analysis (LADA) framework that divided the whole feature space into local patches. Instead of maximizing the trace ratio of the global scatter matrices, a projection matrix was found to maximize the ratio between the traces of the sum of scatter matrices computed for all local patches [Eq. (11)], thereby capturing essential patterns exhibited locally in the feature space. This algorithm was applied to characterize English writing styles in different geographical regions,\textsuperscript{31} but the use of this technique in classification has not been thoroughly validated.

The focus of this paper is to develop a LADA-based nearest neighbour classifier for lesion delineation from mpMRI obtained using the imaging protocol specified in the consensus guideline.\textsuperscript{20} The results generated by this classifier were subsequently optimized by a number of postprocessing steps that removed isolated regions identified as cancerous and filled holes inside detected regions. These steps essentially incorporated prior information on the lesion size and topology into the localization framework. Preliminary results from this study have been previously published in a conference paper.\textsuperscript{32} The current paper substantially extends the conference paper, with a postprocessing algorithm introduced to improve the delineation results generated based on LADA, several additional subjects for evaluation and additional experiments to evaluate the improvement in delineation accuracy attributable to DCE and the proposed postprocessing techniques as well as the sensitivity of delineation accuracy to the prostates used in tuning model parameters.

2. MATERIALS AND METHODS

2.A. Image acquisition and preprocessing

Thirteen subjects with prostate cancer histologically confirmed on previous biopsies were imaged by a 3T GE Discovery MR750 (GE Healthcare, Waukesha, WI, USA) with an endorectal coil (Prostate eCoil, Medrad Inc., Warrendale, PA, USA). Clinical T2W, DW, and DCE MR images were acquired as previously described\textsuperscript{33} for each patient with the following acquisition parameters. T2W 2D fast spin-echo: TR: 4–9 s, TE: 158–163 ms, slice thickness: 2.2 mm. DCE spoiled gradient-recalled echo: TR: 5.6–5.9 ms, TE: 2.1–2.2 ms, flip angle: 15°, 90-s intervals, slice thickness: 2.8 mm. DW 2D echo-planar: TR: 4 s, TE: 70–77 ms, slice thickness: 3.3–3.6 mm, b-value: 600–800. ADC images were generated from DW images on the MR750 console. Images were assessed using ClearCanvas Workstation 7.1 (ClearCanvas Inc., Toronto, Canada) and interpreted by four observers (one radiology resident and three radiologists with 5, 6, 2.5, and 2.5 yr of experiences in prostate MRI assessment) following the Prostate Imaging-Reporting and Data System (PI-RADS) detection guidelines (Version 1).\textsuperscript{30} Each observer delineated lesions that were equivocally, likely, and highly likely to be clinically significant (PI-RADS of 3–5, respectively) and assigned a PI-RADS score to each delineated lesion on T2W, DW, and DCE MR images separately.

Images for each patient were then registered by an expert observer and resampled to standardize the in-plane resolution and slice thickness. The in-plane pixel size is 0.5 × 0.5 mm and the slice thickness is 3 mm after resampling, with the peripheral zone of each gland represented by approximately 20,000 pixels. In this study, regions with PI-RADS ≥ 3 marked by any radiologist on any of the three images were considered cancerous, resulting in a binary classification available on a pixel-by-pixel basis. Our proposed pixel-based cancer localization technique was trained and validated using this pixel-based expert classification.

2.B. Pixel-based feature extraction

We extracted the following features for each pixel. The parentheses show the number of features associated with each pixel:

(1) Grayscale values (9): As prostate lesions typically appear as homogeneous low-intensity regions in T2W images and are associated with low ADC values, gray levels in T2W and DCE images were extracted to train and validate the proposed algorithm. As DCE MR
images were generated in sequence, each pixel is equipped with multiple grayscale values representing temporal signal variation after the injection of a contrast agent.

(2) Sorted grayscale values in the neighborhood (16): For the T2W and ADC images, grayscale values in the eight neighbouring pixels were obtained and sorted in the ascending order. The reason that we chose to sort the grayscale values here was to make the feature and the lesion localization result rotation invariant (i.e., the same region should be detected as cancerous even though the images are rotated).

2.C. Linear discriminant analysis (LDA)

Linear discriminant analysis (LDA) separates two or more classes of high-dimensional data points by finding a projection matrix to maximize a cost function quantifying the inter-class difference in relation to the intraclass variability. A commonly used cost function is the trace ratio cost function, and the development of the current algorithm was based on this function. Mathematically, the \( N \times D \) dimensional data points in the training set are represented by a \( D \times N \) matrix \( X = [x_1, x_2, \ldots, x_N] \). Each data point is represented by a \( D \)-dimensional column vector in \( X \) and belongs to a class \( c_i \) with \( i \in \{1, 2, \ldots, c\} \). Our application is a two-class problem (i.e., \( c = 2 \)). We define \( N_i \) to be the total number of data points in \( c_i \), \( \mu_i \) to be the mean of all data points in \( c_i \), and \( \mu \) to be the mean of all data points. The \( D \times D \) within- and between-class scatter matrices, \( S_w \) and \( S_b \), respectively, are defined as follows:

\[
S_w = \sum_{i=1}^{c} \sum_{x \in c_i} (x - \mu_i)(x - \mu_i)^T, \quad (1)
\]

\[
S_b = \sum_{i=1}^{c} N_i(\mu_i - \mu)(\mu_i - \mu)^T, \quad (2)
\]

For later development of the LADA algorithm, \( S_w \) and \( S_b \) are expressed in terms of \( X \):

\[
S_w = XL_hX^T, \quad (3)
\]

\[
S_b = XL_hX^T, \quad (4)
\]

where \( L_w \) and \( L_b \) are \( N \times N \) matrices with:

\[
L_w = I - \frac{1}{N_i} I \quad \text{and} \quad L_b = I - \frac{1}{N_i} I. \quad (5)
\]

\( A_w \) and \( L_b \) are defined as follows: If \( x_m \) and \( x_n \) are in same class, \( A_w_{mn} = 1/N_i \) and \( L_b_{mn} = 1/N_i - 1/N \). Otherwise, \( A_w_{mn} = 0 \) and \( L_b_{mn} = -1/N_i \). The \((d_1, d_2)\)th component of \( S_w \) are the within-class covariances \((\sum_{x \in c_i} x_kd_1x_kd_2)\) summed across all classes, where \( x_kd_1 \) and \( x_kd_2 \) are the \( d \)th component of the data point \( x_k \) and the class mean \( \mu_k \), respectively. The identity matrix in Eq. (5) accounts for the first term and \( A_w \) accounts for the second term. In the definition of \( L_b \), the terms associated with \( 1/N_i \) accounts for the group means and those associated with \( 1/N \) accounts for the mean of the entire dataset.

LDA finds a \( D \times d \) matrix \( W \) that projects each \( D \)-dimensional data point to a corresponding \( d \)-dimensional data point with \( D \gg d \) that maximizes the trace ratio cost function. Mathematically, \( Y = W^TX \), with the columns of the \( d \times N \) matrix \( Y \) representing the projected \( d \)-dimensional data points. The optimal \( W^* \) is represented by the following equation:

\[
W^* = \arg \max \frac{Tr(W^T S_b W)}{\sum_{w, w=1}^{W} Tr(W^T S_b W)} = \arg \max \frac{Tr(W^T X L_h X^T W)}{\sum_{w, w=1}^{W} Tr(W^T X L_w X^T W)} = \arg \max \frac{Tr(Y L_h Y^T)}{\sum_{w, w=1}^{W} Tr(Y L_w Y^T)}, \quad (6)
\]

in which we used Eqs. (3), (4), and \( Y = W^TX \). The last term in Eq. (6) was associated with a constraint of \( W^TW = I \) to ensure uniqueness of the solution. This equation serves as a building block of the LADA algorithm as will be shown in the next section.

2.D. Locality alignment discriminant analysis (LADA)

A disadvantage of LDA is that \( S_w \) and \( S_b \) are built globally based on the entire training set. The model would better capture the local structure of the training data if the whole feature space is divided into local patches. LADA consists of the patch-by-patch optimization and the global alignment steps, which are described in detail below. A generalization of this scheme to a number of dimensionality reduction algorithms was presented by Ref. [35].

2.D.1. Patch-by-patch optimization

This step establishes a patch for each of the \( l \) data points and its \( K-1 \) nearest neighbours, thereby forming \( l \) patches with \( K \) data points. For each data point \( x_i \), we denote its \( K-1 \) nearest neighbours by \( x_{i1}, x_{i2}, \ldots, x_{ik-1} \). The \( K \) data points within the patch associated with \( x_i \) are represented as columns in the \( D \times K \) matrix \( X_i = [x_i, x_{i1}, x_{i2}, \ldots, x_{ik-1}] \). Using the results established in Eq. (6), the cost function to be minimized in this patch-by-patch optimization is:

\[
\frac{Tr(Y_i L_{hi} Y_i^T)}{Tr(Y_i L_{wi} Y_i^T)}, \quad (7)
\]

where the definitions of \( Y_i, L_{hi}, L_{wi} \) are described in detail in Section 2.C, but now the application of the LADA algorithm is limited to the patch represented by \( X_i \). The number of points in each patch \( K \) was required to be tuned as described in Section 2.G.

2.D.2. Global alignment

This step optimizes the sum of the cost function [Eq. (7)] associated with the \( l \) patches available. The solution can be expressed in the similar format as Eq. (6), except
that now the matrices $L_h$ and $L_w$ depend on the groupings of the $l$ patches. Expressing the sum of the $l$ cost functions in the format of Eq. (6) would not only provide a better comparison between LDA and LADA, but would allow the same procedure used for maximizing the trace ratio in Eq. (6) to be directly applied to optimize the cost function associated with LADA. A major challenge is to find a way to express $Y_i$ associated with each patch in terms of the low-dimensional representation of the entire set of data points, denoted by $Y$ as described in Section 3. Zhang et al. $^{35}$ defined a $l \times K$ selection matrix for each patch $i$, denoted by $S_i$, in order to pick out the $K$ data points in $Y_i$ from $Y$:

$$Y_i = YS_i,$$

with the $pq$ entry of $S_i$ defined by:

$$(S_i)_{pq} = \begin{cases} 1 & \text{if } p = F_i(q), \\ 0 & \text{otherwise} \end{cases}$$

where $F_i = \{i, i_1, i_2, \cdots, i_{K-1}\}$ are the indices of the data points within the patch $X_i$.

With these definitions established, Eq. (7) can be written in terms of $Y$:

$$\frac{Tr(YS_iL_hS_i^TY^T)}{Tr(YS_iL_wS_i^TY^T)},$$

Summation of Eq. (10) for all patches results in the following cost function:

$$\frac{\sum_{i=1}^{l} Tr(YS_iL_hS_i^TY^T)}{\sum_{i=1}^{l} Tr(YS_iL_wS_i^TY^T)} = \frac{Tr\left(Y\left(\sum_{i=1}^{l} S_iL_hS_i^T\right)Y^T\right)}{Tr\left(Y\left(\sum_{i=1}^{l} S_iL_wS_i^T\right)Y^T\right)}$$

$$= \frac{Tr(YL_hY^T)}{Tr(YL_wY^T)},$$

(11)

where $\tilde{L}_h = \sum_{i=1}^{l} S_iL_hS_i^T$ and $\tilde{L}_w = \sum_{i=1}^{l} S_iL_wS_i^T$. The optimal $W^*$ can be written in the same form as for LDA in Eq. (6) and can be efficiently solved:

$$W^* = \arg \max_{W} \frac{Tr(W^T S_h W)}{Tr(W^T S_w W)},$$

(12)

where $\tilde{S}_h = X\tilde{L}_hX^T$ and $\tilde{S}_w = X\tilde{L}_wX^T$.

2.F. Postprocessing to optimize classification accuracy based on LADA

Prior information about lesion size and shape can be applied to increase the specificity and sensitivity in lesion localization. A lesion with a volume smaller than $0.2$ cm$^3$ is not considered as clinically significant by Epstein’s criteria. $^{37}$ For this reason, isolated pixels or a small cluster of pixels that are not “large enough” can be removed to reduce false positives and thereby increase specificity. In the current study, we developed an approach to extract isolated pixels identified as cancerous by LADA. Figure 1 shows an example T2W axial prostate image with cancerous pixels identified by LADA shaded in red. For each point identified as cancerous with coordinates denoted as $p_i$, such as the pixel shown in the inset of Fig. 1(a), a circular ROI centred at $p_i$ with radius $r$ was evaluated, and the point was classified as an isolated point if the percentage of pixels inside this ROI was smaller than $P_{\text{isolated}}$. The two parameters involved, $r$ and $P_{\text{isolated}}$, were optimized for classification accuracy as described in Section 2.G. Figure 1(b) shows the results after the removal of all isolated points.

Secondly, considering a lesion is likely to appear as a solid mass, holes in the detected regions were filled as shown in Fig. 1(c). Finally, the $3 \times 3$ neighbourhood of all detected pixels were filled as an attempt to smoothen the lesion boundary and connect the isolated pixels around the boundary of the lesions. Note that the isolated clusters remained at this stage had not been removed in the previous step because they were close to the main body of the lesion; these lesions should be merged with the main body

![Fig. 1. Illustration of steps involved in the postprocessing procedure. (a) It shows the cancerous region identified by LADA. The inset at the left top corner illustrates the ROI with radius $r$ considered when determining whether or not a point is an “isolated points”. (b) It shows the results after isolated points were removed. (c) It shows the results after filling holes inside the detected ROI. (d) It shows the results after the $3 \times 3$ neighbourhood of all detected pixels were filled. [Color figure can be viewed at wileyonlinelibrary.com]](image_url)
of the lesion to maintain the connectedness of the lesion. The final result of the postprocessing procedure is shown in Fig. 1(d).

2.G. Parameter tuning

The segmentation results generated by the proposed LADA algorithm and subsequent postprocessing procedure depend on the following parameters:

1. $K$, the number of data points in each patch for LADA projection matrix optimization as described in Section 2.D.1.
2. $d$, the number of dimensions in the reduced feature space onto which LADA projects original data points.
3. $r$, the radius of the circular ROI considered in the removal of isolated points as described in Section 2.F.
4. $P_{\text{isolated}}$, the minimum percentage of pixels identified as cancerous by LADA inside a circular ROI for the center of the ROI to be classified as cancerous as described in Section 2.F.

One prostate in the dataset was chosen for parameter tuning and this prostate was excluded in the subsequent validation. One transverse slice in this prostate was used to optimize the LADA projection matrix and classification was subsequently performed for the remaining image slices as described in Section 2.E. The parameters described in the above list were initialized empirically as $K = 50$, $d = 2$, $r = 0.3$ mm and $P_{\text{isolated}} = 0.3$. These parameters were optimized sequentially by changing a single parameter each time while holding the remaining parameters constant. The parameter associated with the minimum sum of false-negative and false-positive rates (FNR and FPR, respectively) was considered optimal. In the current study, $K$ varied from 50 to 300 with an increment of 50, $d$ from 2 to 10 with an increment of 2, $r$ from 0.5 to 5 mm with a 0.5 mm increment, and $P_{\text{isolated}}$ from 0.3 to 0.7 with a 0.1 increment.

2.H. Experimental settings

Multiparametric MR images of 13 patients were involved in this study. Histograms of mpMRI for the 13 patients were standardized according to the algorithm described in Ref. [38]. One prostate was randomly chosen for parameter tuning described in Section 2.G. The optimized parameters were used to localize lesions for the remaining 12 patients using leave-one-out cross-validation. The number of training points in each of the leave-one-out trial is more than 200,000, and the computation and storage requirement for such a huge training set are not supportable by most PCs. To address this issue, training and evaluation for each prostate were performed repeatedly for ten times. The training set in each of the ten trials was randomly chosen that included 25% of pixels located at lesions on each training image slice and pixels located at noncancerous regions that were twice the number of cancerous pixels. A pixel was deemed to be cancerous if it was classified as so in more than or equal to five of ten trials.

To evaluate the sensitivity of the choice of the prostate used for parameter tuning, LADA and the subsequent postprocessing procedure were executed twice, with two different prostates used for parameter tuning. The contribution of the postprocessing techniques described in Section 2.F was quantified by comparing the sensitivity, specificity, and accuracy of lesion segmentation before and after postprocessing. Although DCE is an essential part in the prostate mpMRI protocol, its inclusion leads to serious allergic reactions at a rate of 7/5,000,000. The cost of DCE acquisition is high as patients were required to be monitored for this reaction by a doctor throughout the MRI scanning session. To evaluate how much DCE contributes to the lesion delineation performance of the proposed algorithm, sensitivity, specificity, and accuracy of lesion delineation obtained with and without DCE features were compared. In summary, lesion segmentation was performed in ten settings, which we denote as LDA-woDCE, LDA-wDCE, LADA-P1-woProc-woDCE, LADA-P1-woProc-wDCE, LADA-P1-woProc-wDCE, LIDA-P2-woProc-wDCE, LADA-P1-wProc-woDCE, LADA-P2-wProc-woDCE, LADA-P1-wProc-wDCE, and LADA-P2-wProc-wDCE. P1 and P2 refer to the two prostates used for parameter tuning, wProc and woProc refer to with and without postprocessing, respectively, and wDCE and woDCE refer to with and without DCE features, respectively.

The benefits of lesion-targeted prostate cancer therapies are dependent on the lesion delineation performance in MRI, which has been shown to underestimate prostate lesions substantially.[39] To improve the efficacy of treatments, a treatment margin was applied to fully cover a high percentage of lesions (e.g., 95% in Refs. [40, 41]). Overcontouring could increase the damage to surrounding organs at risk in focal boosting therapies. In this study, we investigated how adding a margin from 1 to 10 mm would improve the lesion detection sensitivity. The result can help determine a treatment margin required to attain a sufficient, but not more than sufficient, coverage of the lesion.

3. RESULTS

Parameters tuning for LADA was performed twice using different prostates as described in Section 2.H. $d = 4$, $K = 200$, $r = 3$ mm and $P_{\text{isolated}} = 0.4$ in the first trial and $d = 4$, $K = 250$, $r = 3.5$ mm and $P_{\text{isolated}} = 0.4$ in the second trial.

Table I lists the sensitivity, specificity, and accuracy attained by the two LDA-based settings and the eight LADA-based settings described in Section 2.H. For each of the LADA settings, leave-one-out cross-validation was performed on 12 prostates with the prostate involved in parameter tuning excluded from validation. The average performance metrics in delineating lesions in 12 prostates based on each of the experimental settings were reported in the right panel of Table I. As these LADA experiments were tuned either by P1 or P2, the validation subgroup varies with experiment.
settings. To make a fair comparison among settings, the performance metrics were averaged over a common subset of prostates that excluded both P1 and P2 and reported in the left panel. Inclusion of DCE features increased the sensitivity by 14–30% and applications of the postprocessing techniques described in Section 2.F increased the sensitivity by 9–16%, whereas the algorithm tuned by different prostates produced sensitivities within a 3% range in four experimental setting pairs, each of which corresponded to the same postprocessing and DCE settings. However, the specificit"
algorithm matched the surrogate ground truth in the remaining three consecutive slices shown in Fig. 4. Figure 5 shows the T2W, ADC, and DCE images acquired at the imaging plane in which the lesion was missed by the algorithm. The missed lesion was delineated by only one of four observers and only on the T2W image. This ROI was considered as an identified lesion in the surrogate ground truth because an ROI delineated by any observer in any modality with PI-RADS score ≥3 was considered an identified lesion, and the lesion in question was scored 4 by the observer who delineated it on the T2W image. In other words, the proposed algorithm agreed with 3 of the 4 observers or 11 of 12 delineations (4 observers/modality × 3 modalities; the observer delineated the missed lesion only in T2W, but not ADC and DCE) in that the missed ROI is not a part of the identified lesion. In essence, the fourth observer disagreed on the extent of the detected lesion along the inferosuperior direction but only on the T2W image. Figure 5(b) shows the T2W image with the area identified by the single observer imposed. The DCE image displayed in Fig. 5(d) is the one that shows the

---

**Fig. 2.** The first, second, and third columns show three example cases for which the proposed algorithm generated good (95%), average (80%), and lower than average (58%) sensitivity, respectively. The first row shows the T2W images, the second row shows the manually delineated regions with PI-RADS score ≥3, the third row shows the region delineated by the LADA-based classifier, and the fourth row shows true-positive detection in red, false-negative region in green, and false-positive regions in blue.
maximum enhancement in the missed region. All the above observations applied to the second missed lesion. Similar to the first case, an observer disagreed on the inferosuperior extension of the lesion and the disagreement occurred only on his observation of the T2W image.

Another missed lesion spanned three imaging slices as shown in Fig. 6 and the algorithm missed the region on the middle slice, which would have been covered with a three-dimensional margin expansion. Figure 7 shows the three image sequences on this slice. The volume estimated from experts’ and algorithm delineation were 0.5 and 0.21 cm$^3$, respectively. The missed lesion was delineated by only one of four observers, but on all three image sequences.

The proposed algorithm was implemented in Matlab 2017a and took approximately 1560 s for computing the projection matrix based on the training set consisting of 14,000–16,000 data points with $K = 200$, 1.2 s for applying the projection matrix on all data points belonging to the testing set and finding the nearest labelled neighbours, and 1 s for completing the postprocessing steps described in Section 2.F. The time required for computing the LADA projection matrix was highly dependent on $K$, the size of the local patch as described in Section 2.G. This computational time increases from 82 to 4367 s when $K$ increases from $K = 50$ to 300.

All experiments were performed in an Intel(R) Xeon(R) E5-2650 v4 CPU @ 2.2 GHz with 8 GB memory.

4. DISCUSSION

While the use of mpMRI was demonstrated to increase the accuracy of tumor identification, the widespread acceptance of this imaging technique has been hampered by the lack of standardization on the acquisition and the interpretation of the images. To address this issue, the ESUR and ACR established consensus guidelines for the imaging protocols and proposed a scoring system, PI-RADS, as an effort to standardize the interpretation and reporting of mpMRI results with a PI-RADS score of $\geq 3$ in each image contrast commonly considered to be the optimal cutoff for cancerous tumors. However, previous studies based on this standard were all performed by manual assignment of PI-RADS score, which is time-consuming and prone to interobserver variability. For this reason, there is a compelling need for an automated tool for delineating prostate lesions from images obtained according to the consensus clinical protocol. The delineation sensitivity, specificity, and accuracy achieved by the proposed algorithm were 75%, 75%, and 75%, respectively. This performance is comparable to that produced by previous mpMRI lesion delineation studies in...
which nonclinical T2 maps were available, which have sensitivities ranging from 64% to 87% and specificities from 78% to 90%.25-27,45

One of the manifestations of the curse of dimensionality in machine learning is that data points can become uniformly distributed when the number of dimensions increases. The Euclidean distance from a point’s closest neighbour approaches that from its furthest data point with a dimension of 15 according to Ref. [30]. For this reason, the dimensionality of the feature space was required to be reduced before the application of the nearest neighbour classifiers. Inspired by the patch alignment concept,35 LADA was developed to maximize the ratio between the traces of the sum of the scatter matrices computed for all local patches in the feature set.31 As the between- and within-class scatter matrices computed in each patch did not consider data points far away from this neighbourhood, LADA is expected to better adapt to the local structure of the data. The algorithm was applied to characterize the difference between the English writing styles exhibited in different geographical regions.31 However, since cross-validation was not performed in the writing style study, it was not clear whether LADA truly provides a better classification of different regional English styles than LDA or whether it was overtrained on the available data. The current study is the first study demonstrating that the nearest neighbour classifier provides higher classification performance on the reduced space generated by LADA than that generated by LDA.

![Fig. 5. The (a) T2W, (c) ADC, and (d) DCE images acquired at the imaging plane in which the lesion shown in the first column of Fig. 4 was missed by the algorithm. Although the missed lesion [pointed to by an arrow in (b)] was delineated by only one of four observers and only on the T2W image as shown in (b), it was deemed cancerous since regions marked by any of the observers were considered to be a lesion according to the rule by which surrogate ground truth classification was generated (Section 2.A). In other words, the proposed algorithm agreed with 3 of the 4 observers or 11 of 12 delineations (4 observers/modalitiy x3 modalities) in that the missed ROI was not a part of the identified lesion. [Color figure can be viewed at wileyonlinelibrary.com]](image)

![Fig. 6. This figure shows a lesion with an estimated size of 0.50 cm³ spanning three consecutive image slices. The first row shows consecutive T2W transverse images. The second and the third rows show the same images but with lesions detected by the expert observers and algorithm superimposed. The algorithm missed the lesion located at the image slice shown in the second column (pointed to by an arrow in the second row). More details related to the observers’ delineation of this image slice are provided in Fig. 7. [Color figure can be viewed at wileyonlinelibrary.com]](image)
In addition, it was a priority to evaluate the algorithm's delineation sensitivity, specificity, and accuracy. Although the proposed algorithm agreed with 3 of the 4 observers or 9 of 12 delineations (4 observers/modality × 3 modalities) in that the missed ROI was not a part of the identified lesion. [Color figure can be viewed at wileyonlinelibrary.com]

Our study had a number of limitations. The first limitation is related to the small sample sizes involved in this investigation in which we pilot this approach. As this study involved four observers who segmented lesions and assigned PI-RADS scores on each of the three MR images, evaluation of 13 prostates already took considerable time. While we acknowledge that the intersubject variability may not be sufficiently represented by the study population, it is appropriate to evaluate the proposed algorithm in a pilot study before an assessment is performed in a larger population. In fact, previous lesion delineation algorithms were evaluated in patient populations of similar sample sizes.\(^\text{25,26}\)

Another limitation of the study is that the evaluation was performed only in the peripheral zone of the prostate.\(^\text{46,47}\) The evaluation was designed as such because a vast majority (75%) of cancerous tumors develop in the peripheral zone.\(^\text{46,47}\) In addition, it was a priority to evaluate the algorithm on peripheral zone tumors in this pilot study as these tumors are associated with a larger odds of pathologic adverse outcomes, such as extracapsular extension, seminal vesicle invasion, and lymphovascular invasion.\(^\text{48}\) Although we expect that the proposed algorithm would also be able to delineate lesions at the transition zone, lesion delineation should be done separately in the peripheral and transition zones as the mpMRI features associated with lesions at the two zones would likely be different. The capability of the algorithm in delineating lesions in the transition zone is required to be thoroughly validated in a future study.

Similar to previously described binary classifiers developed for lesion delineation from mpMRI,\(^\text{25,26}\) the proposed algorithm is capable of localizing and providing size estimations for cancer foci, but do not predict the PI-RADS score that indicates the likelihood that these foci are clinically significant. We are currently developing a regression model that will predict the PI-RADS score distribution over the entire prostate. The availability of the objectively predicted PI-RADS score distribution will further optimize diagnosis accuracy.

5. CONCLUSION

A classification framework was developed to localize and delineate prostate lesions from mpMR images obtained in standard clinical protocol specified in the consensus guideline.\(^\text{20}\) The delineation sensitivity, specificity, and accuracy are 75%, 75%, and 75%, respectively, which are comparable to those generated by previous mpMRI lesion delineation algorithm in which nonclinical T2 maps were available. The construction of T2 map requires the image acquisitions in ten echo times, leading to long acquisition times that could not be afforded in clinical practice. The ability to delineate lesions based on standard clinical protocol efficiently afforded by the proposed framework will potentially contribute to the acceleration of the adoption of mpMRI in clinical practice.

ACKNOWLEDGMENTS

Dr. Chiu is grateful for funding support from the Basic Research Free Exploration Program of the Science Technology and Innovation Committee of Shenzhen Municipality, China (Project No. JCYJ20160428155118212), the Research Grant Council of the HKSAR, China (Project No. CityU 11205917), and the City University of Hong Kong Strategic Research Grants (Nos. 7004425 and 7004617).

CONFLICT OF INTEREST

None declared.

Author to whom correspondence should be addressed. Electronic mail: bcychiu@cityu.edu.hk.

REFERENCES

7. Durkan GC, Greene DR. Elevated serum prostate specific antigen levels in conjunction with an initial prostatic biopsy negative for carcinoma: who should undergo a repeat biopsy?. BJU Int. 1999;83:34–38.


