Multiparametric Dynamic Contrast-Enhanced Ultrasound Classification of Prostate Cancer

R.R. Wildeboer¹, A.W. Postema², L. Demi¹, M.P.J. Kuenen³, H. Wijkstra¹,² and M. Mischi¹
¹Lab of Biomedical Diagnostics, Eindhoven University of Technology, The Netherlands
²Academic Medical Center, Amsterdam University Hospital, The Netherlands
³Philips Research, Eindhoven, The Netherlands

Abstract—Although prostate cancer (PCa) is the most common non-cutaneous form of cancer among Western men, available diagnostic imaging methods are not yet sufficiently reliable to avoid systematic biopsy. In this work, we aim at improving the accuracy of transrectal dynamic contrast-enhanced ultrasonography (DCE-US) for PCa localization by combining local perfusion and dispersion parameters. To this end, ten of these parameters were extracted pixel-by-pixel from 45 DCE-US recordings distributed over 19 patients that were scheduled for radical prostatectomy. Based on 43 benign and 42 malignant histologically-confirmed regions of interest, we produced multiparametric maps using a Gaussian Mixture Model (GMM) algorithm. All possible combinations of one to four parameters were evaluated to select the most suitable subset of parameters. We also tested the GMM algorithm's ability to determine the classification confidence for each pixel and the impact of excluding low-confidence pixels from the images. An accuracy and negative predictive value of 81% and 83%, respectively, were obtained, which improved after pixel exclusion. Even though extended validation on a larger patient group is recommended, multiparametric DCE-US shows high potential in localizing PCa and might become an important tool for guiding targeted biopsy or planning of focal treatment.

Keywords—prostate cancer; dynamic contrast-enhanced ultrasound; multiparametric classification; machine learning

I. INTRODUCTION

Prostatic malignancies are the most prominent cancer occurring in American men, accounting for 26% of the new cases and about 10% of the deaths each year [1]. Due to the lack of a sufficiently reliable imaging method to detect and localize prostate cancer (PCa), currently a definitive diagnosis can only be made after a ≥10 core systematic biopsy procedure [2]. However, this method has known risks and limited sensitivity. This results in a frequent occurrence of biopsy-related complications [3] and a substantial number of PCa lesions found only after repeated biopsy [4]. Accurate imaging is thus important to reduce our reliance on systematic biopsy by identifying suspicious regions for targeted biopsy [5]. In addition, it is crucial for planning, monitoring and follow-up of focal treatment [6].

PCa is a heterogeneous and multifocal disease [7]. Depending on cancer type, grade, and origin, it might appear very differently in known imaging modalities. In B-mode ultrasonography (US), approximately 30–40% of the tumors are isoechoic [8], and conventional magnetic resonance imaging (MRI) generally suffers from low specificity [9]. In recent years, multiparametric MRI was developed to cope with this problem. Combining information from different MRI modalities yielded an average sensitivity of 74% and a specificity of 88% [10]. Nevertheless, there are still difficulties in the interpretation of scoring systems and a standardized protocol is not yet established.

In this work, we focus on a multiparametric combination of the data from transrectal US measurements. US imaging has certain advantages over MRI, such as its cost-effectiveness and practicality at bedside [8]. Furthermore, the use of intravenously-injected ultrasound contrast agents enables the visualization of perfusion and vascular fraction [11]. Prostatic malignancies exhibit angiogenesis and neovascularization during their progression to clinical significance [12], and are therefore recognizable by changes in the microvascular architecture. As Doppler US imaging is generally unable to capture the small flows revealing these changes, dynamic contrast-enhanced US (DCE-US) is increasingly used for this purpose [11]. Due to the ambiguous effect of angiogenesis on blood flow [13], however, visual inspection of DCE-US for biopsy targeting is not a viable alternative to systematic biopsy.

To characterize prostate tissue, more detailed assessment of UCA kinetics is required. Over the years, the contrast-enhancement (i.e., the time-intensity curve or TIC) has been quantified over time at each pixel by the wash-in rate, time-to-peak (PT), peak intensity (PI), and area under the curve (AUC) [14]–[16]. In addition to these perfusion-related parameters, the dispersive behavior of the UCA bolus can also be assessed. To this end, each TIC is either fitted by a convective dispersion model [17] or subjected to a similarity analysis with its neighboring TICs [18]. For the multiparametric analysis of DCE-US presented here, ten different parameters that relate to perfusion or dispersion are taken into account.

II. MATERIALS AND METHODS

A. Data acquisition and histopathology

DCE-US recordings were performed in nineteen patients that were scheduled for radical prostatectomy at the Academic Medical Center, University of Amsterdam (The Netherlands). The procedure was approved by the local ethics committee and all participants signed an informed consent. For imaging, 2.4
nL of SonoVue® microbubble suspension (Bracco, Italy) was intravenously administered, marking the start of a 5-minute recording. Images were obtained using an IU22 scanner (Philips Healthcare, Bothell, WA) equipped with either a C10-3v or a C8-4v transrectal ultrasound probe, depending on availability. The prostatectomy specimens underwent histopathologic examination as described by [19]. Based on the histopathology, 85 regions of interest (ROIs) were manually drawn onto the B-mode ultrasound images to mark malignant (42 ROIs) and benign (43 ROIs) tissue. In total, 45 imaging planes were included for the analysis.

B. Classification procedure

Both perfusion- and dispersion-related parameters were extracted from the recordings using Matlab (MathWorks 2015b, Natick, MA). The adopted perfusion parameters were the appearance time (AT, in s, where the TIC reaches 5% of the PI), the PI itself (in a.u.), the PT (in s), the time from bolus arrival to peak (wash-in time, WIT, in s), and the full width half maximum (FWHM, in s). Fitting-based parameters were extracted following the method described in [17] and yielded the AUC (in a.u.), the mean transit time (μ, in s), the skewness parameter (k, in s³), and the ratio between diffusive and convective time (λ = k/μ). Finally, similarity analysis was conducted using the pre-processing and computations featured in [18], allowing us to obtain two dispersion parameters, namely, spatiotemporal correlation (r) and coherence (ρ) [18], [20].

In Gaussian Mixture Model (GMM) classification, a mixture of normal distributions is computed to describe the class-specific distribution of observations in multiparametric space. In our case, the observations are the pixels in the training set, and the classes are the malignant and benign pixels. Using these distributions, we can compute the probability of each new observation belonging to either of the two classes. Subsequently, the observation is classified as the class for which it has the highest probability. In the current work, the GMM classification algorithm is based on an Iterative Expectation-Maximization algorithm and all parameters are scaled to their 90th percentile to ensure equal weighting.

In addition, assessment of classification confidence was implemented. Because this confidence intuitively depends on the relative difference in class probabilities, the confidence level (P) is defined as

\[ P = 2 \frac{p_A}{(p_A + p_B)} - 1. \]  \hspace{1cm} (1)

Here, p_A and p_B are the probabilities of the observation belonging in the most probable or the other class, respectively. This measure ranges from 0 to 1, with 1 being the highest possible confidence.

C. Classification procedure

The proposed multiparametric analysis was evaluated based on a leave-one-out procedure for each prostate. The performance in terms of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was calculated. The accuracy represents the percentage of correctly classified observations in the test group, whereas the sensitivity and specificity reflect the correct classification percentage for malignant and benign observations, respectively. The PPV and NPV quantify the percentage of malignantly and benignly classified pixels that are correct [21].

The most suitable set of parameters for the multiparametric analysis was determined by evaluating the accuracy of every possible multiparametric set of one to four parameters. Subsequently, the multiparametric performance was compared to the best performing single perfusion and dispersion parameters, which were analyzed based on their receiver operating characteristic curve [21]. We also tested the impact of excluding pixels with a low confidence level from the analysis.

### III. RESULTS

The combination of r, μ, κ, and PT yields the highest accuracy. As depicted in Table 1, all performance measures are improved with respect to the best single-parameter approach for perfusion (WIT) and dispersion (r). Using the confidence interval to exclude low-confidence pixels, it is possible to considerably increase the performance of the classification maps. Figure 1 depicts the accuracy, NPV, and

<table>
<thead>
<tr>
<th>Performance</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIT</td>
<td>r</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>72</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>75</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>68</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>76</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>67</td>
</tr>
</tbody>
</table>

![Fig. 1. Performance of the multiparametric analysis based on r, μ, κ and PT after pixel exclusion based on classification confidence. The blue square reflects the accuracy, the red triangle the NPV, and the green circle the PPV. The bars indicate the malignant (dark) and benign (grey) pixels still included in the analysis.](image)
Fig. 2. Multiparametric analysis of three prostates: (a, e, i) B-mode grayscale images of the prostates with benign (green) and malignant (red) ROIs in overlay; (b, f, j) multiparametric classification maps showing non-suspicious and suspicious regions in green and red, respectively, of which the transparency scales with the confidence level; (c, g, k) multiparametric classification maps, excluding all pixels with $P < 0.5$; and (d, h, l) corresponding histopathological slices with malignant regions marked in red. The multiparametric analysis was based on $r$, $\mu$, $\kappa$, and PT.

PPV of our classification approach when increasing the confidence threshold for inclusion. It is noted that the excluded pixels were equally distributed over benign and malignant regions and that pixel exclusion up to 50% did not lead to any region or prostate being disregarded.

In Figure 2, the classification results of three prostates are shown as an example of the multiparametric maps to be expected. It can be noticed that the pixels excluded from the analysis are generally located in the border region between malignant and benign areas. The locations of the ROIs and the results of histopathology can be found in the first and last column, respectively.

IV. DISCUSSION

In this work, a GMM-based approach has been used to multiparametrically characterize prostate tissue on transrectal DCE-US scans. Histopathological verification allowed us to determine ROIs that were subsequently used to train the classification algorithm to mark suspicious malignant and unsuspicious benign areas. A prostate-based leave-one-out validation revealed that the multiparametric approach has an improved accuracy with respect to a single-parameter use of DCE-US measurements.

Our multiparametric validation, however, was limited by the small patient group. PCa lesions are known to be differently represented in imaging, depending on type, grade, stage or location. A larger patient group provides a better representation of the full PCa spectrum, possibly enabling us to discriminate low-risk and high-risk PCa and, therefore, also reduce the likelihood of misclassification for those lesions that most deviate from the training set average. As the microvascular density is found to be significantly higher for higher Gleason scores [22], grade-specific classification is expected to be feasible. Furthermore, the error margin adopted in the correlation of DCE-US maps with histopathology did not allow the inclusion of small lesions ($<0.5\, \text{cm}^2$). Even though these lesions are generally considered to be clinically irrelevant [19], their classification would contribute to the clinical decision-making.

It was found that the most accurate results are obtained using a parameter subset comprising $r$, $\mu$, $\kappa$, and PT, therefore combining both dispersion- and perfusion-related parameters. Since $\mu$ and $\kappa$ are the two shape parameters in the local density random walk model for local dispersion-convection kinetics [23], we appreciate that this combination adds most to $r$. Whereas the WIT is the best performing single-parameter quantifying perfusion, its similarity to $\mu$ rendered it redundant in the multiparametric analysis. The use of PT in inter-patient validation is often complicated due to its dependence on circulation time; however, in this case its inclusion led to better delineation of the malignant and benign areas in combination with the first three parameters.

In addition, the GMM algorithm’s ability to indicate the classification confidence has been investigated. It was demonstrated that excluding low-confidence pixels from the multiparametric maps increases the classification performance without affecting malignant areas, benign areas or specific patients in particular. Although we recommend evaluating also
the use of other classification algorithms for multiparametric DCE-US of the prostate, alternative algorithms that are frequently used (e.g., neural networks, support vector machines) do not generally exhibit such a straightforward confidence measure.

V. CONCLUSIONS

In the diagnosis and treatment of PCAs, there is an increasing demand for suitable and reliable imaging modalities. Targeted biopsy strategies based on imaging are being developed to reduce our reliance on systematic biopsy. Moreover, sufficiently reliable visualization techniques are required for planning, monitoring, and follow-up of focal therapies. Our results suggest the multiparametric combination of contrast-ultrasound features to increase the accuracy of PCa localization compared to the use of individual parameters alone. To further develop this technique, also additional ultrasound parameters as well as diagnostic information from other techniques might be included in the classification procedure. As 3D DCE-US analysis is feasible [24], a 3D classification approach can also be foreseen to accelerate the clinical workflow and, therefore, facilitate the clinical uptake of the method. Furthermore, the proposed method could be applied in other types of malignancy.

ACKNOWLEDGMENT

This research was conducted in the framework of the IMPULS2-program within the Eindhoven University of Technology. This study has also received funding by an unrestricted grant from the Dutch Cancer Society (#UVA2013-5941) and the European Research Council Starting Grant (#280209).

REFERENCES