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Machine Learning for Multiparametric Ultrasound Classification of Prostate Cancer using B-mode, Shear-Wave Elastography, and Contrast-Enhanced Ultrasound Radiomics

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***Abstract*—The diagnosis of prostate cancer (PCa) is still based on systematic biopsy, but is increasingly developing towards an imaging-driven approach. In particular, multiparametric magnetic resonance imaging (MRI) is receiving increasing attention over the last few years. In light of MRI-related issues concerning costs, practicality, and availability, we investigate a multiparametric ultrasound (mpUS) approach. We propose and test a machine-learning-based strategy that automatically combines B-mode ultrasound, shear-wave elastography (SWE), and dynamic contrast-enhanced ultrasound (DCE-US) features. To this end, automatic zonal segmentation by deep learning, model-based feature estimation (related to contrast-agent perfusion and dispersion), radiomic feature extraction, and a random-forest-based pixel-wise classification were combined. The method was trained and validated against histopathologically-confirmed benign and malignant regions of interest in 48 PCa patients, in a leave-one-patient-out cross-correlation fashion. The mpUS classification algorithm yielded a region-wise area under the Receiver Operating Characteristics (ROC) curve of 0.75 and 0.90 for PCa and significant (i.e., Gleason $\geq$4+3) PCa, respectively. In comparison, the best-performing single parameter (i.e., DCE-US-based contrast velocity) reached a performance of 0.69 and 0.76 in terms of the ROC curve area. In particular the combination of perfusion-, dispersion-, and elasticity-related features were favored in the classification. Even though validation on a larger patient group is required, we have demonstrated the technical feasibility of automatic mpUS for PCa localization. Further development of mpUS might lead to a valuable clinical option for robust, ultrasound-driven PCa diagnosis.**

***Index Terms*—Machine Learning, Prostate Cancer, Multiparametric Ultrasound, Shear-Wave Elastography, Dynamic Contrast-Enhanced Ultrasound**

I. Introduction

Prostate cancer (PCa), the most prevalent non-skin malignancy among American and European men [1], [2], currently relies strongly on blood tests, rectal examination, and systematic biopsy [3]. The complications and risks of in particular the latter procedure [4], [5] have led to wide-carried research into an image-driven diagnostic strategy. In recent years, magnetic resonance imaging (MRI) has shown promise for the localization of PCa (and therefore as guidance for image-based targeted biopsy) when performed in a multiparametric fashion [6], [7]. As such, imaging is now being integrated in the guidelines of the PCa diagnostic pathway. Nevertheless, MRI has important drawbacks in terms of costs, bed-side practicality, and availability. Moreover, the cognitive radiologic scoring systems used for multiparametric combination exhibit steep learning curves and known disconcordance between operators [8].

In this work, we study the potential of a multiparametric ultrasound (mpUS) approach. Ultrasound modalities such as shear-wave elastography (SWE) and dynamic contrast-enhanced ultrasound (DCE-US) (with quantification software) have been introduced for PCa imaging with encouraging results and there are indications that their combination might improve the overall PCa localization performance [9]–[11]. In fact, SWE assesses the tissue stiffness [12], whereas DCE-US reflects the vascular characteristics [13], [14], which are complementary features. Moreover, in contrast to a scoring system, we examine the use of radiomics [15] and machine learning [16] to extract useful, complementary mpUS information for PCa imaging.

II. Materials and Methods

A. Data acquisition

An mpUS procedure (i.e., consisting of greyscale ultrasound, SWE and 2-minute DCE-US with 2.4 mL SonoVue® (Bracco, Milan, Italy) contrast agents) was performed in 48 patients that were referred for radical prostatectomy. All acquisitions were carried out at the Martini Clinic Prostate Cancer Centre (University Hospital Hamburg Eppendorf, Germany) with an Aixplorer® ultrasound scanner (SuperSonic Imagine, Aix-en-Provence, France) and an SE12-3 endocavity probe. For each prostate, two-dimensional mpUS imaging was performed at the base, mid and apex sections of the gland. A clinical trial protocol paper (NCT03091231) has been published on the procedure [17].

After surgery, the resected prostate was histopathologically examined [18], digitally reconstructed [19], and subsequently mapped to the imaging [20]. Aware of registration errors,

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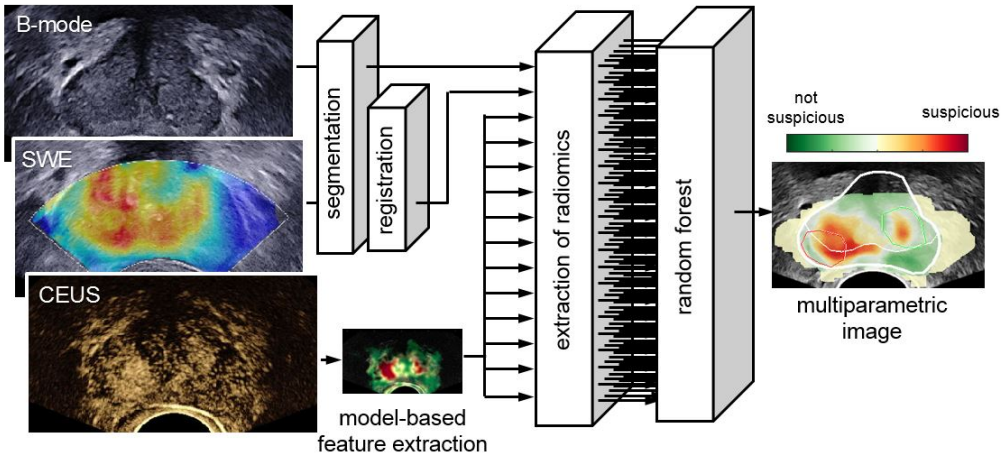

Fig. 1: Schematic overview of the classifier architecture, featuring B-mode ultrasound, shear-wave elastography, and contrast-enhanced ultrasound, subsequent model-based feature and radiomics extraction, and random-forest classification.

regions of interest were drawn in benign, insignificantly-malignant (i.e., Gleason 3+3), moderately-malignant (i.e. Gleason 3+4), and significantly-malignant (i.e., Gleason $\geq$4+3) regions.

B. Classification algorithm architecture

The general outline of the classification algorithm architecture is illustrated in Fig. 1. For each modality, the prostate was automatically located and zonally segmented [21]. The outer contours were subsequently used to register the images. Calcifications were localized and excluded in the further classification pipeline. Twelve different contrast-ultrasound dispersion features were extracted from the DCE-US cine-loop [22]–[25], including contrast velocity, dispersion, and wash-in time. Together with the Young's modulus estimated by SWE and the greyscale echogenicity values, these features were used for radiomic extraction. The relative value to the image median, the multiscale entropy, and the variance in a $\sim$2-mm kernel were used as radiomic parameters reflecting heterogeneity and asymmetry.

Machine learning was implemented as a random-forest classifier with all radiomic features serving as input variables. In total, the forest consisted of 1,000 trees that were each trained on a small subset of the training samples. We enforced generalizability by limiting the tree size and randomly excluding a said amount of prostates for the training of each tree. Moreover, we grew two distinct sets of forests for the two prostate zones, which typically show different characteristics in imaging [14], [26]. The final pixelwise multiparametric maps, which reflected the forest agreement on PCa classification, were postprocessed with a $\sim$2.5-mm median filter.

C. Validation methodology

A leave-one-out strategy was adopted for cross-validation, allowing us to calculate the overall Receiver Operating Characteristic curve areas (ROC-AUC) of the multiparametric score in a region-of-interest-wise fashion. For statistical validation, we used a Wilcoxon rank sum test with p-value thresholds of $<$0.05 (*) and $<$0.005 (**) to depict statistical significance.

III. Results

The multiparametric approach outperformed the single-parametric outcomes of SWE as well as DCE-US. Whereas the contrast velocity, the best performing DCE-US parameter, yielded an ROC-AUC of 0.69 and 0.76 for PCa and significant PCa versus benign regions, and SWE only reached 0.62 and 0.73, mpUS resulted in ROC-AUCs of 0.75 and 0.90. As depicted in Fig. 2, the multiparametric score also shows some correlation with cancer aggressiveness.

IV. Discussion and Conclusion

The multiparametric radiomic machine-learning approach for mpUS as presented in this work was shown to outperform single-parametric PCa imaging. This improvement is likely a shared contribution of the use of radiomics and the multiparametric strategy, combining complementary features. These results are in line with research in multiparametric MRI [6], earlier work on multiparametric combination of DCE-US features [27], and mpUS based on cognitive scoring [28].

Moreover, it was shown that the mpUS multiparametric scores also reflected cancer aggressiveness. It should be stressed that clinically insignificant PCa has been defined in multiple ways in the literature [29], [30]; we therefore distinguish insignificant, moderate, and significant cancer to fully examine the ability of mpUS to distinguish aggressiveness.

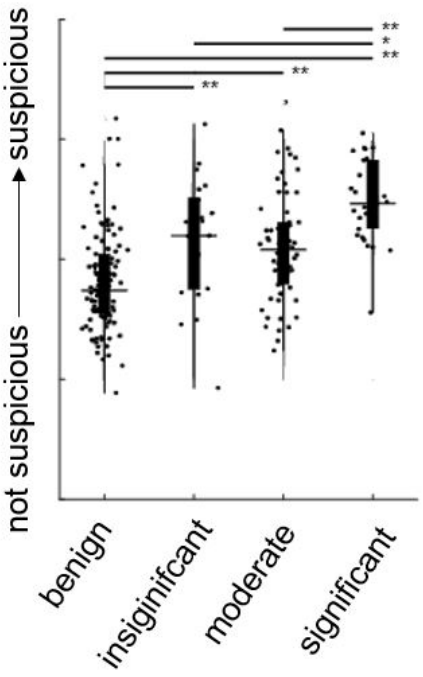

Fig. 2: Multiparametric score distribution over benign and malignant regions of interest of increasing PCa grade (i.e., insignificant: Gleason 3+3, moderate: Gleason 3+4, significant: $\geq$4+3).

Remarkably, insignificant PCa is generally considered more suspicious in terms of mpUS score than moderate PCa. This may reslut from the fact that only patients with very large insignificant tumours are selected for surgery whereas the greater part of insignificant PCa patients (who received less radical treatment) could not be included in the study due to absence of whole-gland pathology.

Limitations of this study reside in the dataset size and the single-centre set-up of the study. In order to have radical prostatectomy specimens as a ground truth, we could not include patients without PCa, which might have biased the presented performances. In the future, a full range of intensity-based, morphological, texture-based, and statistics-based features could be considered [31], [32] as well as other new model-based parameters such as SWE viscoelasticity [33] and contrast-agent entropy [34].

Nevertheless, this work clearly demonstrates the technical feasibility of an mpUS approach based on radiomics and machine learning. We believe that further research in an extended dataset, possibly in three dimensions [35]–[37], might allow further clinical implementation in the future.

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