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Review

Advances in radiology and pathology of prostate cancer: a review for the pathologist

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Summary
Multiparametric magnetic resonance imaging (mpMRI) has improved systematic prostate biopsy procedure in the diagnosis of clinically significant prostate cancer (csPCa) reducing the number of unnecessary biopsies; numerous level one evidence studies have confirmed the accuracy of MRI-targeted biopsy, but, still today, systematic prostate biopsy is recommended to reduce the 15-20% false negative rate of mpMRI. New advanced imaging has been proposed to detect suspicious lesions and perform targeted biopsies especially when mpMRI cannot be performed. Transrectal ultrasound (TRUS) modalities are emerging as methods with greater sensitivity and specificity for the detection of PCa compared to the traditional TRUS; these techniques include elastography and contrast-enhanced ultrasound, as well as improved B-mode and Doppler techniques. These modalities can be combined to define a novel ultrasound approach: multiparametric ultrasound (mpUS). More recently, Micro-ultrasound (MicroUS) and prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) have demonstrated to be sensitive for the detection of primary prostatic lesions resulting highly correlated with the aggressiveness of the primary prostatic tumour. In parallel, artificial intelligence is advancing and is set out to deeply change both radiology and pathology. In this study we address the role, advantages and shortcomings of novel imaging techniques for Pca, and discuss future directions including the applications of artificial intelligence–based techniques to imaging as well as histology. The significance of these findings for the practicing pathologist is discussed.

Key words: prostate cancer, fusion prostate biopsy, mpMRI, PSMA PET/CT, artificial intelligence

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Introduction

Screening [1] and case-finding protocols [2] for prostate cancer (PCa) diagnosis are based on PSA and digital-rectal examination [3] but the risk of overdiagnosis is estimated in about 50% of the cases, therefore the main goal is to detect only clinically significant PCa (csPCa) (ISUP grade group > 2); in this respect, Active surveillance has become an alternative to radical treatment of low/very low risk prostate cancer (PCa), reducing the risk of overtreatment and improving quality of life of the patients [4]. Over the past decade, multiparametric magnetic resonance imaging (mpMRI) has improved systematic prostate biopsy procedure in the diagnosis of csPCa reducing the number of unnecessary biopsies; a lot

of level one evidence studies [5-9] have confirmed the accuracy of MRI-targeted biopsy, but, still today, systematic prostate biopsy is recommended in addition to targeted biopsy to reduce the 15-20% false negative rate of mpMRI [10]. Although the in-bore targeted biopsy seems to be more accurate to diagnose csPCa in comparison with MRI/TRUS (transrectal ultrasound) fusion biopsy (61 vs. 47%) (Fig. 1) no clinically significant difference has been reported in multicentric clinical trials comparing cognitive vs. fusion vs. in-bore targeted biopsy [9]. In addition, mpMRI false negative rate has not been reduced by new fusion platforms nor by improved mpMRI tecnology, therefore other imaging procedures have been evaluated, in clinical trials, to detect prostate targets.

New advanced ultrasound modalities are emerging as methods with greater sensitivity and specificity for the detection of PCa compared to the traditional TRUS; these techniques include elastography and contrast-enhanced ultrasound, as well as improved B-mode and Doppler techniques. These modalities can be combined to define a novel ultrasound approach, multiparametric ultrasound (mpUS) [11,12]. More recently, Micro-ultrasound (MicroUS) has also emerged as a promising imaging technology for PCa diagnosis [12]. At the same time, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has demonstrated to be sensitive for the detection of primary prostatic lesions apart clinical metastases [13]; moreover, tumour uptake, which represents PSMA expression, has been highly correlated with the aggressiveness of the primary prostatic tumour [14-18].

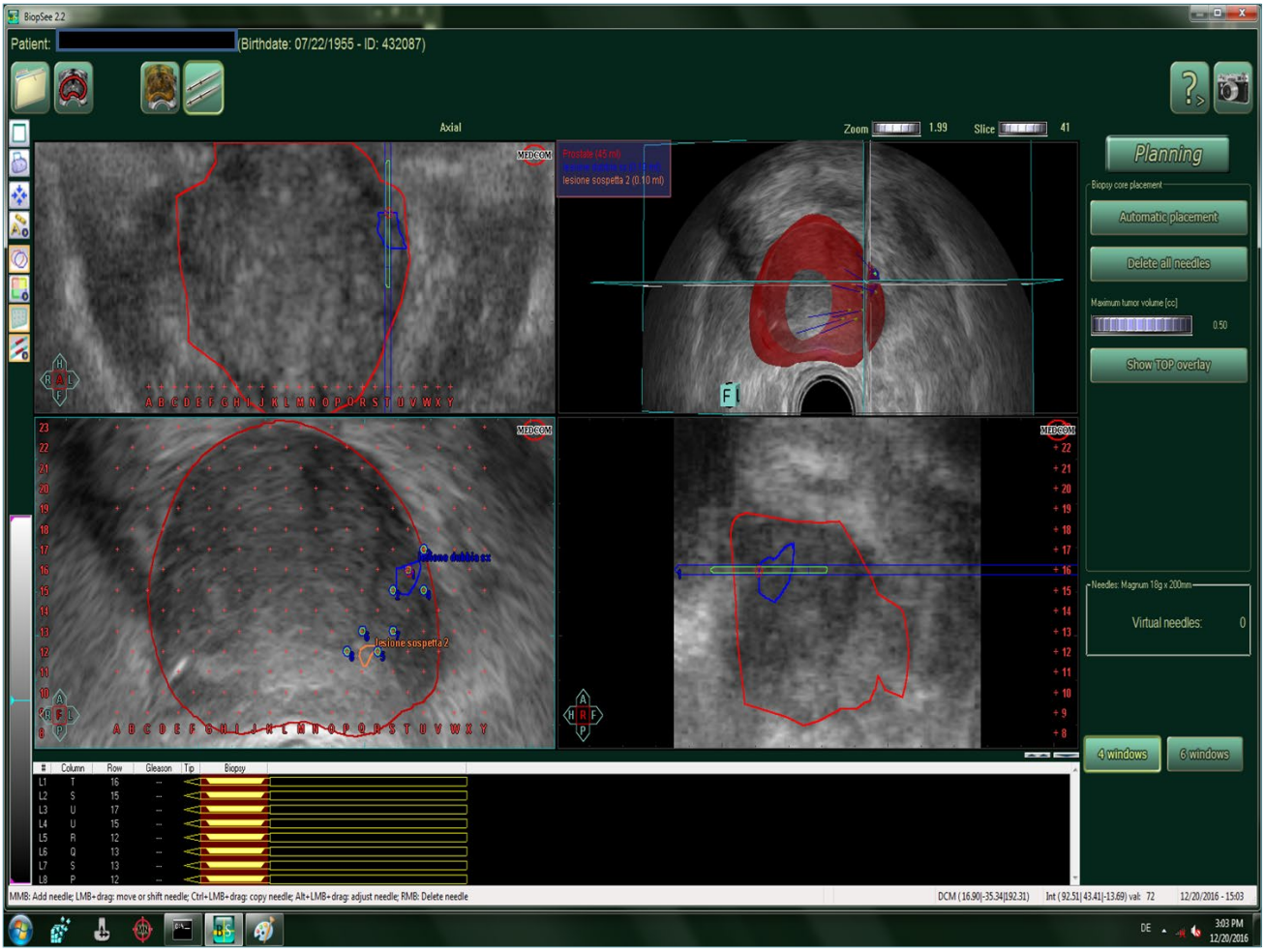

Figure 1. Tridimensional and computerized transperineal prostate MRI/TRUS fusion biopsy "Biopsee® system": coronal plane (top left);axial plane plus targeted cores (top right, bottom left), longitudinal plane with targeted core into suspicious area (bottom left)

Multiparametric ultrasound

The ideal approach to the diagnosis of PCa should be to detect significant disease performing a limited number of targeted biopsy cores improving the accuracy of standard TRUS by mpUS; clinical studies have shown that mpUS increases sensitivity by 13-59% in detecting PCa [19,20]. In the last years, TRUS has been enriched by the introduction of tridimensional and computerized images (Fig. 2) and by the use of contrast media and transrectal elastosonography (TRES) [21], which allow better characterization of intraparenchymal microvasculature. After the unsuccessful results of ultrasound contrast medium [22], recently, the microbubble ultrasound contrast agents (UCA: Sonovue®, Definity®, Imagent®) have improved flow detection in small vessels to distinguish normal from pathological tissue [23-24].

Elastosonography measures the degree of distortion of ultrasound beam under the application of an external force that is displayed and scored over the B-mode image in a colour scale that corresponds to tissue elasticity. Recently, elastosonography has improved by the introduction of Shear Wave Elastosonography (SWE) that is a quantitative method that evaluate local tissue elasticity resulting much less operator dependent; the sensitivity and specificity of TRES range from 71-82% to 60-95% [21] in definitive specimen of men submitted to radical prostatectomy.

Contrast-enhanced transrectal ultrasound (CEUS) uses contrast agents that enable improved detection of low volume blood flow beyond the scope of Doppler ultrasound. Ultrasound contrast agents are gas-filled microbubbles with diameters comparable to erythrocytes allowing passage into the microvasculature; the microbubbles are more reflective than blood in the vascular lumen improving flow detection with ultrasound. A limitation of CEUS is related with the transient perfusion of the prostate in the arterial phase (unlike the liver and kidney, the prostate gland has less intense perfusion). In addition, benign prostatic hyperplasia (BPH) increases the size and vascularity of the transition zone potentially masking perfusion of a malignancy. A prospective trial of 1024 patients reported an increase in PCa detection using CEUS (28.7%) compared to systematic biopsy (25.3%); subgroup analysis demonstrated a higher yield of csPCa detection using CEUS in patients with a PSA level ≤ 10.0 ng ml or prostate volume from 30 to 60 ml [25]. On the other hand, a metanalysis of 16 papers and 2642 patients confirmed that CEUS is a promising tool in cancer detection, however, it is not sensitive enough to avoid systematic biopsy, showing a low detection rate for PCa included between 15.5 and 32%. Recently, Liu et al. developed a nomogram prediction model based on Prostate Imaging Reporting and Data System (PI-RADS) and CEUS for predicting csPCa in men with PSA 4-10 ng to avoid unnecessary biopsy [26].

Strain elastography (SE) is performed using the endorectal probe and applying compression to the prostate gland. Compression and decompression cycles are performed through the rectal wall by the transducer. A color-coded map or elastogram is generated from speckle comparison between compression/decompression cycles. The elastogram is overlaid on the B-mode image for interpretation, stiff tissues are color-coded in blue and soft tissues are shown in red. Compression of stiffer tissues such as PCa demonstrate less variation in the volume of deformity compared to normal parenchyma, the deformation (strain) is depicted by the elastogram. Several studies have demonstrated that SE provides added value to TRUS imaging, particularly in the context of higher Gleason grade cancers [27]. A meta-analysis including 508 patients demonstrated a pooled sensitivity and specificity for prostate cancer detection with SE of 72 and 76%, respectively [28]. The limitations of SE include skilled user dependency, heterogenous interpretation of the elastogram and false results from benign inflammatory prostate pathologies. SE is reported to miss low-grade cancers and has a lower detection rate for anterior cancers limiting its use as the sole modality to determine patient suitability for prostate biopsy. Shear-wave elastography (SWE) assess stiffness of the

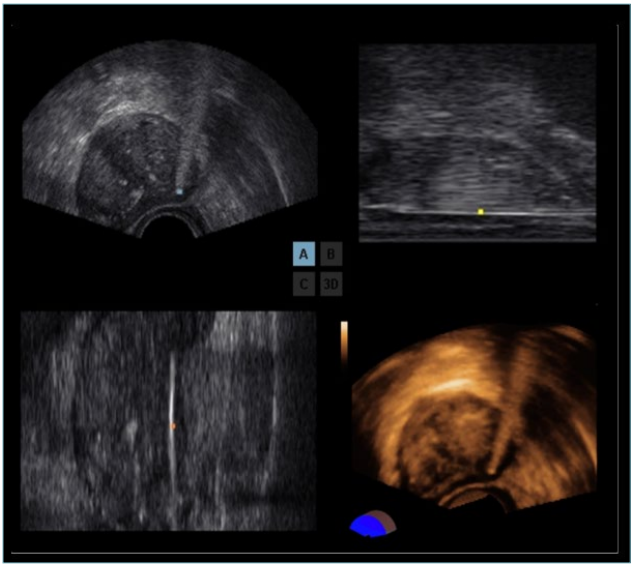

Figure 2. Tridimensional and computerized images of prostate: prostate biopsy. Top to bottom, left to right: axial plane;sagittal plane;coronal plane;3D image.

prostate tissue by measuring the velocity of the shear wave as it passes through tissue. The shear wave is produced from an ultrasound beam using the acoustic radiation force to propagate a velocity. Shear wave speed is related to elasticity and measurements of the shear wave speed are displayed on a color map that is the opposite to that used for SE - stiff tissue is color-coded red and soft tissues are blue. To produce SWE, compression of the prostate tissue must be avoided to reduce artefactual measurements. SWE is carried out in real time from base to apex to identify lesions suspicious for cancer amenable to targeted biopsy. The application of SWE is to characterize abnormal areas seen at B-mode TRUS examination, perform a targeted biopsy of a suspicious area and detection of stiff lesions not identified on other imaging modalities. Early studies of SWE have shown a correlation between stiffness and Gleason score. A meta-analysis of nine studies showed pooled results indicating that SWE is a useful technique to differentiate cancer from benign tissue, the pooled sensitivity being 86% and the specificity 89% 29). Compression prior to SWE from B-mode imaging can alter results particularly in patients with larger glands making it more difficult to perform B mode imaging without compression at the rectal wall. Another technical challenge of SWE is the limit of the acoustic radiation force extending to the anterior gland in large prostates. Similar to SE, SWE can contribute to false results arising from benign processes, such as calcifications.

In conclusion, mpUS has emerged as a promising toolkit for the detection and targeted biopsy of csPCa; these methods add valuable information in the diagnostic pathway of PCa and could help to overcome the ever increasing burden on MRI and its limitations, such as lack of access, variability in acquisition, interpretation and false negative of MRI, and real-time visualization for accurate targeted biopsy.

It is expected that further advances in ultrasound technology and use of modalities such as artificial intelligence will enable effective implementation of mpUS in clinical practice [30,31].

Microultrasound

High resolution MicroUS is a novel imaging modality that represents a further advance of B-Mode TRUS. This technology (ExactVu 29 MHz system) developed by Exact Imaging (Toronto, Ontario, Canada), which has received regulatory approval in the European Union (CE Mark), United States (FDA), and Canada (Health Canada medical device license) for visualization and biopsy of the prostate [32]. This technical improvement is based on two differences with conventional TRUS: frequency of 29 MHz and higher crystal density along the transducer (512 vs. 128 crystals). The high resolution of the MicroUS system permits visualization of the ductal anatomy and cellular density, resulting in a more detailed view of the prostate anatomy compared to TRUS. Differences in cell density detected by MicroUS results in increased sensitivity for detection of tissue patterns related to PCa [33]. As a consequence, MicroUS has emerged as a promising new imaging device for targeted biopsy, with the potential to improve sensitivity and negative predictive value for csPCa, mainly due to its capacity of visualizing and targeting under real-time lesions suspicious for PCa. Prostate Risk Identification using Micro-UItrasound “PRI-MUS” grading system was proposed and validated to assess the risk of PCa for targeted biopsy with the MicroUS platform [34]; PRI-MUS is analogous to PI-RADS scoring system for suspicious areas on mpMRI, since both use a 1-5 scale for increasing scale suspicion of cancer on biopsy. However, in contrast to PI-RADS, the PRI-MUS protocol is designed to take advantage of the real-time nature of ultrasound to be applied live during real-time TRUS biopsy. PRI-MUS is based on B-mode assessment and is not multiparametric. The ExactVu instrument is optimized for imaging prostates of various sizes with three imaging presets to optimize transmit pulse parameters, receive aperture, and signal processing parameters to ensure high resolution. For MRI lesions visible on MicroUS, visually directed real-time targeted biopsy can be performed; multiple studies have also shown that the sensitivity of MicroUS is comparable to that of mpMRI for detection of csPCa [35,36]. A recent multicentre analysis on 1040 patients showed that MicroUS had comparable or higher sensitivity for csPCa compared to mpMRI; in this study, MicroUS and mpMRI sensitivity was 94 vs. 90%, NPV was 85 vs. 77%, and specificity 22 vs. 22%, respectively [37]. A meta-analysis on accuracy of MicroUS in detecting csPCa (769 patients) showed that MicroUS displayed sensitivity, specificity, diagnostic odds ratio and area under the summary ROC curve of 0.91, 0.49, 10 and 0.82, respectively [38]. In a meta-analysis comprising 13 studies and 1125 patients the detection rate of csPCa and insignificant PCa, as well as the overall detection rate of PCa were similar between MicroUS-guided and mpMRI-targeted prostate biopsy [39]. Wiemer et al. [40] showed additional benefit of adding MicroUS to mpMRI and systematic mapping, owing to its potential to detect csPCa that may be invisible on mpMRI. Basso Dias et al. [41] compared the detection rate for PCa of Micro-US vs. mpMRI index lesion showing a sensitivity of 76.5 vs. 65.1%, specificity of 76.6 vs. 93.4%, negative predictive value of 85.6 vs.83.2%, positive predictive value of 64.1

vs. 84.3% and diagnostic accuracy of 76.6 vs. 81.8%. Lughezzani et al. [42] assessed diagnosis of csPCa with MicroUS in a cohort of 320 patients with a positive MRI (PI-RADS ≥3) and showed a 2.6% improvement in csPCa detection by adding MicroUS targets to that of MRI targets and systematic biopsy. Furthermore, they concluded that MicroUS and MRI appear to provide complementary information that could be combined to maximize the detection of csPCa. Recently, MicroUS and mpMRI have been evaluated in men enrolled in AS protocols and showed a sensitivity of 94.1% and 100%, and an NPV of 88.9% and 100%, respectively, in detecting ISUP ≥ 2 PCa [43,44].

Studies have shown that there may be discrepancies in the quality of software-based fusion assisted targeting; this reinforces the benefit of targeting under real-time visualization achieved with MicroUS. While results of multiple studies have cemented the role of MicroUS in detection of csPCa, increased attenuation of the ultrasound beam at higher frequency can lead to limited depth of penetration, and this can therefore limit the diagnostic accuracy of the current generation MicroUS device in assessment of anterior transition zones in large prostates. Imaging enhancements to improve image quality in the anterior prostate and a modified PRI-MUS scale addressing regions outside the peripheral zone should address this discrepancy and provide further improvement in MicroUS performance. Moreover, robust studies aiming to determine the learning curve of MicroUS and the interobserver agreement in the PRI-MUS score are needed. It should be emphasized that as MicroUS is a novel imaging technology and the data on accuracy for PCa detection are still preliminary [45]. Many of the published studies are retrospective in nature, some with small number of patients, and substantial heterogeneity between cohorts included in the meta-analysis. The results of ongoing prospective trials are awaited and will help to assess role of MicroUS in the diagnosis of csPCa. Multicenter randomized control trials comparing MicroUS vs. MRI-targeted biopsy will also help to establish the role of MicroUS in the diagnostic algorithm for detection of csPCa. The Micro-Ultrasound versus MRI (OPTIMUM), 3-arm randomized controlled trial [45], will evaluate the role of 29 MHz micro-ultrasound in guiding prostate biopsy in men with clinical suspicion of prostate cancer; the trial investigate whether microUS alone, or in combination with mpMRI, provides effective guidance during prostate biopsy for the detection of clinically significant prostate cancer (csPCa) for biopsy naïve subjects.

In definitive, micro-ultrasound has demonstrated similar sensitivity to detect csPCa as mpMRI; unlike mpMRI, micro-ultrasound is performed in the office, in real-time during the biopsy procedure, and so is expected to maintain the cost-effectiveness of conventional ultrasound, but larger studies are needed before these results may be applied in a clinical setting.

PSMA PET/CT

In the last years, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has demonstrated to be sensitive for the detection of PCa [46,47]; PSMA inhibitors conjugated with the radionuclides Gallium 68 (^{68}Ga) and fluoride 18 (^{18}F) have been evaluated in clinical practice for the diagnosis of PCa. The tumour uptake, which represents PSMA expression, is highly correlated with the aggressiveness of the primary prostatic tumour [48,49]. Although ^{68}Ga-PSMA-PET/CT is recommended to improve the clinical staging of high-risk PCa and disease recurrence [50-55] recently, PSMA PET/CT has been proposed for the diagnosis of PCa by targeted biopsy [56-59] and in men enrolled in Active Surveillance protocol [60-63]. A PET/CT scan suspicious for PCa results from a combination of factors, such as homogeneity and intensity of PSMA expression, tumor volume, and grade. The presence of focal uptake on PSMA-PET/CT, Stadardized Uptake Value (SUVmax), and the maximal dimensions of PET-avid lesions have been correlated with the presence of csPCa (Fig. 3). Emmett et al. [64] evaluated the clinical significance of intraprostatic patterns of PSMA activity, proposing a 5-point PRIMARY score to optimize the accuracy of ^{68}Ga-PSMA PET/CT for csPCa; a 5-level PRIMARY score was assigned on the basis of analysis of the central read: no pattern (score of 1), diffuse transition zone (TZ) or central zone (not focal) (score of 2), focal TZ (score of 3), focal peripheric zone (PZ) (score of 4), or an SUVmax of at least 12 (score of 5). The Primary study demonstrated a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of csPCa in the presence of a PRIMARY score > 3 (high-risk patterns) equal to 88%, 64%, 76%, and 81%, respectively. There is a range of proposed cutoffs to detect csPCa from SUVmax 3.15 to SUVmax 9.1 65,66); Demirci et al. [67] in 141 patients submitted to radical prostatectomy showed that the SUVmax values were significantly higher in high-risk patients compared those in low-risk patients 18.9 ± 12.1 vs.7.16 ± 6.2). Kalapara et al. [68] compared the accuracy of ^{68}Ga-PSMA PET/CT with mpMRI in 205 men who underwent radical prostatectomy and showed an accuracy of 96% vs. 91% for the detection of csPCa. Shen et al. [69] showed that a SUVmax cut-

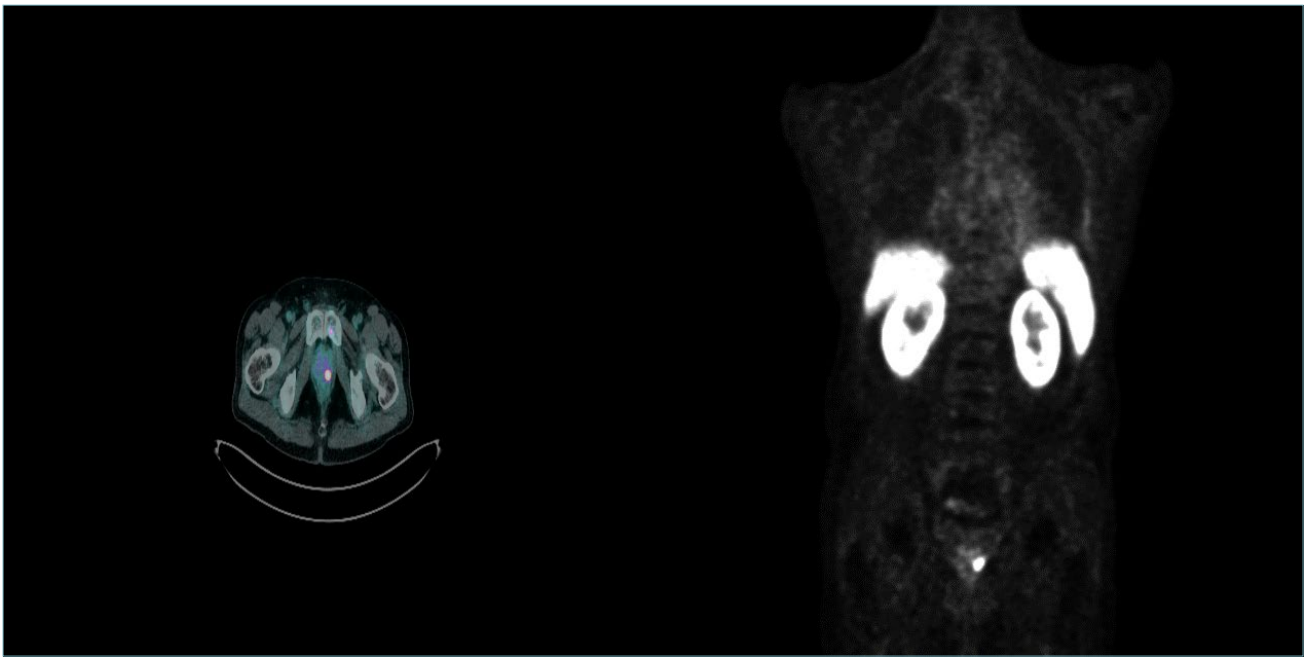

Figure 3. ^{68}GaPSMA PET/CT nodular area of the left prostatic lobe (left) with a SUVmax of 24.5 in absence of distant metastases (right). Targeted biopsy demonstrated a ISUP Grade Group 3 prostate cancer. Abbreviations: ^{68}GaPSMA: ^{68}Gallium prostate-specific membrane antigen;PET/CT: positron emission tomography/computed tomography;SUVmax: standardized uptake value;ISUP: International Society of Urological Pathology.

off of 5.4 predicted pathological upgrading at definitive histology, showing 91% specificity and 94% negative predictive value. We recently showed in 160 men with median PSA of 11.6 ng/ml that a ^{68}GaPSMA PET/CT with a SUVmax cut-off of 8 had a diagnostic accuracy equal to 100% in the diagnosis of Grade Group ≥3 PCa [65] (Fig. 3). Lopci et al. [70] demonstrated an higher accuracy of PET/CT PSMA in comparison with microUS in the diagnosis of csPCa (83 vs. 61%).

In definitive, ^{68}Ga-PSMA PET/CT evaluation could be proposed in men with clinically suspicious of high risk PCa to perform diagnosis (targeted biopsy) and staging of confirmed PCa; at the same time, ^{68}Ga-PSMA PET/CT improves cost-benefit ratio as a single procedure for the diagnosis and staging of high-risk PCa. Finally, ^{68}Ga-PSMA PET/CT could be suggested in men candidate to prostate biopsy when mpMRI can not be performed (i.e., claustrophobia, cardiac pacemaker, and severe obesity) [71]. Anyway, a learning curve is required to perform an accurate PSMA-guided cognitive prostate biopsy.

Radiological-histological correlation

No imaging technique at present has perfect accuracy in detecting PCa, and the gold standard for diagnosis is represented by histology. A corollary of this observation is that no imaging feature is definitely associated with PCa, and each can give rise to false positives and false negatives that can usually be explained in a deterministic manner.

For example, in mpMRI, prostatitis can be concerning since it shares some imaging features with PCa. Namely, T2W and ADC sequences will show focal hypointensity (without a corresponding hyperintensity in DWI). Furthermore, blood flow to the lesion will be increased and DCE sequences will show enhancement; additionally, locoregional lymphadenopathy can be observed [72]. Prostatic abscesses can be even more concerning, showing DWI hyperintensity in addition to the aforementioned findings.

Other imaging modalities suffer from similar problems. For example, studies on elastography-based assessments in mpUS have shown that stiffness correlates with Gleason grade. Crucially, however, stiffness is also a feature of chronic prostatitis and some benign hyperplastic nodules, giving rise to false positives [73].

PSMA PET/CT, both with ^{68}Ga [74] and ^{18}F [75], has also shown some limited cases of false positives, since PSMA avidity can also be observed in tumors other than PCa (possibly due to cancer neovasculature) as well as in reactive lymph nodes.

This knowledge of the shortcomings of imaging techniques is invaluable for the pathologist. Upon examination of a prostate biopsy, knowledge of which clinical and radiological features prompted the biopsy can help explain the histologic findings in a deterministic way. In other words, the clinical and radiological suspicion for cancer can appear to be discordant with a diagnosis of benignity. In reality, after histopathological analysis and multidisciplinary discussion, all data will usually fit in a coherent explanation for the observed findings.

To further add to the importance of radiological-histological correlation, of histological confirmation, and of multidisciplinary discussion, the prostate can be affected by numerous other neoplasms in addition to acinar adenocarcinoma [76]. Some of these can be treacherous and mimic PCa not only clinically and radiologically, but even histologically, requiring careful examination and ancillary techniques to reach the correct diagnosis [77,78].

Artificial intelligence in prostate imaging and pathology

In recent years, significant advances in artificial intelligence and computer-aided diagnosis have improved the diagnosis of PCa, both radiologically and histologically [79,80].

Artificial intelligence-based tools have shown promise in improving the accuracy and speed of radiologists by automating or improving the human workflow [81,82] Similarly, some dated problems in PCa histopathology such as a relatively low interobserver and intraobserver concordance on measurements and Gleason grading [83-85] are being mitigated by these new techniques. Notably, AI-based systems hold the promise of augmenting the diagnostic capabilities of pathologists by providing them with decision support, thereby mitigating interobserver variability and offering a more standardized and reproducible diagnostic framework. Recently, a free and open-

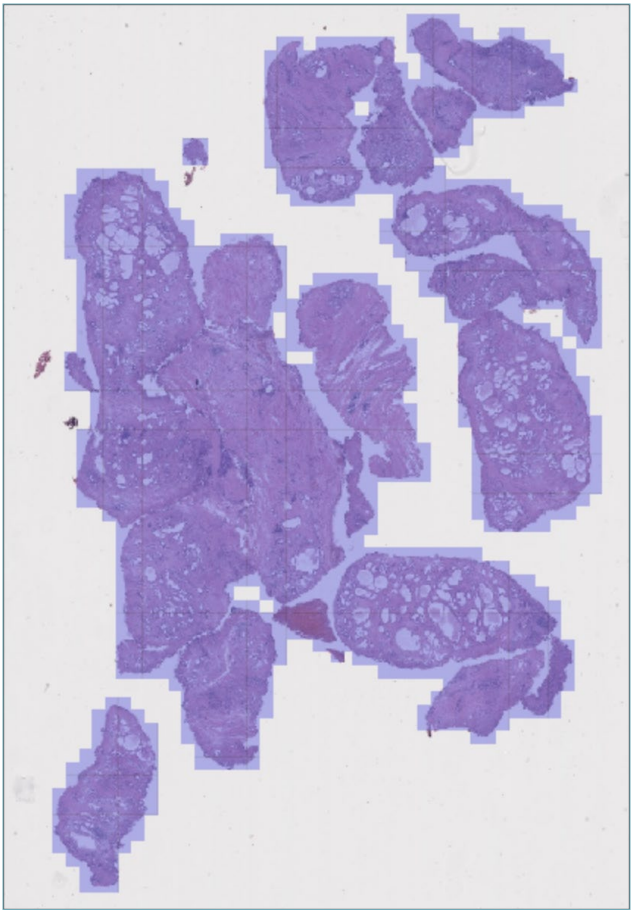

Figure 4. AI-assisted diagnosis in a slide of benign prostatic hyperplasia on transurethral resection material. All fields are correctly classified as negative (blue) by the model.

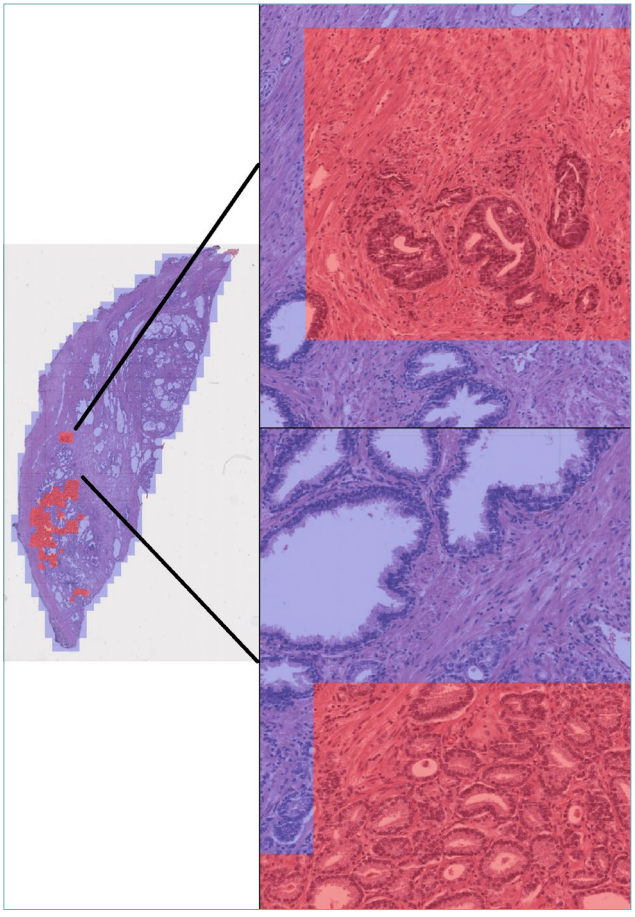

Figure 5. AI-assisted diagnosis in a slide from a radical prostatectomy. The model correctly classifies cancerous areas in red.

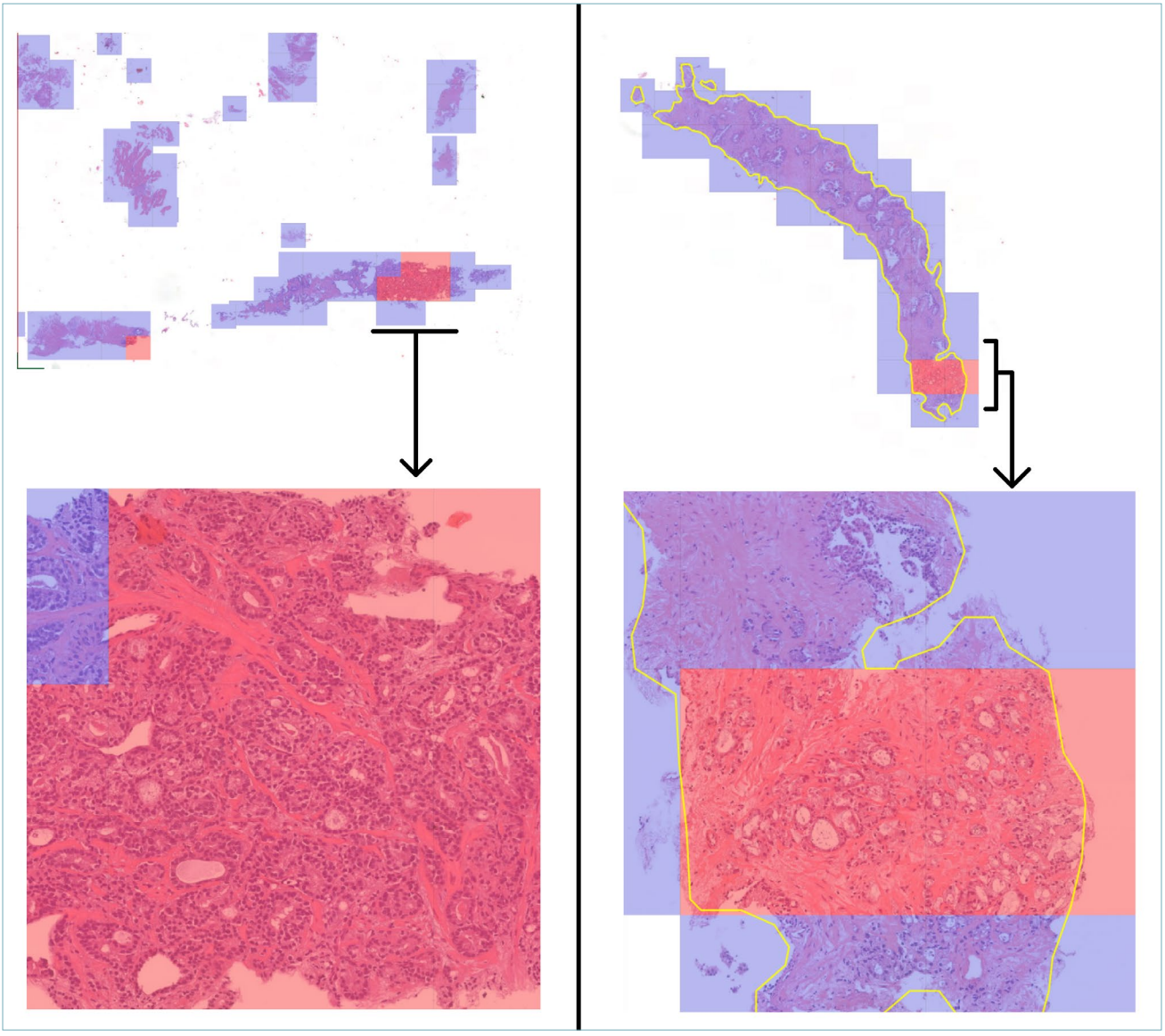

Figure 6. AI-assisted diagnosis in two slides from prostate needle biopsy. The model correctly classifies cancerous areas in red.

source platform for rapid and user-friendly inference was released, allowing convenient usage of WSInfer [86] in QuPath [87] (Figs. 4-6) (demonstration video: 📽 **https://youtu.be/0Z589zWIFQQ**).

Not only do whole-slide images allow pathologists to accurately quantify and measure microscopic features, but, for example, even the pre-analytical variability responsible for stain variation can be reduced using normalization techniques. These techniques have been shown to increase the speed and confidence of pathologists when dealing with poorly stained slides [88].

Similarly, the diagnostic accuracy of pathologists can be increased by a system that classifies each slide as benign or suspicious for cancer, and in the latter case also pinpoints the location that has the greatest probability of harboring cancer) [89]. Nevertheless, as these innovations continue to evolve, critical considerations pertaining to data quality, algorithm interpretability, and the indispensable role of expert pathologists in training and validating these models merit diligent attention [90].

Conclusion

Multiparametric MRI still today remains the gold standard [91] to diagnose csPCa reducing the number of

unnecessary biopsies; conversely, the mpMRI/TRUS fusion platforms have not reached an easy and accurate performance to do targeted biopsy. Among mpUS the use of micro-US seems to improve diagnostic accuracy of standard TRUS in the diagnosis of csPCa; the procedure allows to perform an office-based TRUS-guided biopsy allowing to reduce the cost of mpMRI evaluation. On the other hand, ^{68}Ga-PSMA PET/CT seems to improve PCa diagnosis showing a good diagnostic accuracy as a single procedure for the diagnosis and staging of high-risk PCa, but further randomized studies including a greater number of patients should be performed before the use in clinical practice. Each imaging technique has its own advantages and shortcomings of which the radiologist, the urologist and the pathologist should be aware. Advances in these techniques and in artificial intelligence are bound to play a major role in the improvement in the diagnostic performance of csPCa.

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Conflicts of interest

The authors declare no conflict of interest.

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Authors contribution

Conceptualization: PP, FF. Supervision: PP, FF. Manuscript-drafting: PP, AC. Manuscript-review and editing: all authors.

Ethical consideration

As a review article, the present study is exempt from ethical approval.

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