Prostate ultrasound: back in business!

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Abstract

The use of grey scale prostate ultrasound decreased after the implementation of magnetic resonance imaging (MRI) for the diagnosis and evaluation of prostate cancer. The new developments, such as multiparametric ultrasound and MRI-ultrasound fusion technology, renewed the interest for this imaging method in the assessment of prostate cancer. The purpose of this paper was to review the current role of prostate ultrasound in the setting of these new applications. A thorough reevaluation of the selection criteria of the patients is required to assess which patients would benefit from multiparametric ultrasound, who would benefit from multiparametric MRI or the combination of both to assist prostate biopsy in order to ensure the balance between overdiagnosis and underdiagnosis of prostate cancer.

Keywords: prostatic neoplasms; image-guided biopsy; magnetic resonance imaging; ultrasonography

Introduction

The diagnosis of prostate cancer (PCa) using transrectal greyscale ultrasound (US) is limited only to the identification of the hypoechoic lesions in the peripheral zone of the prostate, which account for 50-70% of the PCa cases [1]. A normal US does not necessarily mean that PCa is absent, but the lack of visibility on US is usually associated with a low grade cancer. On the other hand, the biopsy of a suspect lesion has a two times higher likelihood of diagnosing clinically significant PCa (high volume and grade) [2].

Systematic US-guided prostate biopsy is performed in a randomized manner according to the European Association of Urology Guidelines [3], which leads to the underdiagnosis of an important rate of clinically significant PCa [4]. In this setting, magnetic resonance imaging (MRI) has emerged as a new standard for the diagnostic evaluation and staging of prostate cancer [5]. Prostate MRI assesses four sequences: T2 weighted imaging (T2-WI), dynamic contrast enhancement (DCE-MRI), diffusion weighted imaging (DWI-MRI) and spectroscopy. As a result, the use of T2-WI in combination with at least two functional techniques (DCE, DWI, spectroscopy) is referred to as multiparametric MRI (mpMRI). The anatomical sequence (T2-WI) is used for the detection of prostate cancer, whereas the functional techniques offer information regarding the perfusion and metabolic profile of the lesion [6].

Aiming to standardize the report and techniques for mpMRI, the European Society of Urogenital Radiology introduced the Prostate Imaging Reporting and Data

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System (PI-RADS), which was recently updated and is used to estimate the risk for the presence of clinically significant cancer (1 – very low; 5 – very high) [7]. Vargas et al showed that PI-RADS version 2 can diagnose up to 95% of prostate cancer foci with a volume higher than 0.5 ml [8]. Other authors confirmed the importance of MRI in the diagnosis of prostate cancer and reported a negative predictive value for mpMRI of 97% for the presence of aggressive prostate cancer [9]. Furthermore, the PROMIS trial has shown that the use of mpMRI as a triage test at the first presentation might avoid 27% of prostate biopsies [10].

Although these results seem very promising, there is significant variability in the published studies [11], depending of the number of cases and the experience of the radiologist. Lower volume centers report a negative predictive value of mpMRI as low as 63% [12] and a moderate rate of interreader agreement, even after the implementation of PI-RADS version 2 ($\kappa=0.478$) [13].

Furthermore, there are intrinsic limitations of mpMRI. Approximately 80% of tumors smaller than 0.5 ml are missed by mpMRI, even though they are clinically significant (Gleason score $\geq 4+3$) [5] and tumor foci ≥ 0.5 ml that contain Gleason 4 with a cribriform pattern remain undiagnosed in 64% of cases [14].

Although mpMRI has shown multiple advantages for the diagnosis and characterization of prostate cancer, its use in everyday clinical practice is still limited and the results are impaired by the differences in MRI protocols and reporting, and the experience and training of the radiologists.

As a result, the new US techniques that can be used for the assessment of prostate disease (contrast-enhanced ultrasound and elastography) and the new role of ultrasound in association with MRI for the guidance of prostate biopsy (cognitive and fusion) restore its importance for the diagnosis of prostate cancer.

The present paper aims to review the current role of US for the diagnosis of PCa and prostate biopsy.

Conventional transrectal grey scale ultrasound

Prostate greyscale US has a low sensitivity and specificity for the detection of PCa. The suspicion is raised by the presence of a hypoechoic area, but this appearance is characteristic only for about 60% of PCa. The rest of PCa nodules are isoechoic, therefore they are usually missed at US [15,16]. Furthermore, only 17-57% of the hypoechoic areas at greyscale US are diagnosed as malignant at biopsy [17].

Prostate US has an important role in performing prostate biopsy by guiding the needle towards the peripheral

zone of the prostate, but the low sensitivity in detection of the malignant nodules does not always allow a targeted biopsy. As a result, the standard prostate biopsy is performed in a randomized manner. A number of technical aids have been developed in order to improve the detection rate of PCa and ensure a targeted biopsy: color and power Doppler US, contrast-enhanced US (CEUS), elastography, multiparametric US, and magnetic resonance imaging.

New ultrasound techniques

Color and power Doppler US

Color and power Doppler US allow the assessment of tumor angiogenesis. It is considered that the microvascular density is high in neoplasms and is associated with a high grading and a negative prognosis. On the other hand, benign conditions that associate enhanced vascularity, like infection or inflammation, might lead to a false positive result. However, studies have shown that color Doppler can increase the PCa detection rate of grey scale US with 12% [18].

Power Doppler ultrasound is a more sensitive examination, allowing the identification of blood vessels of 1 mm. But the tumor angiogenesis vessels are much smaller, with a caliber of 10-15 microM, thus limiting their identification [19-20].

Still, a number of studies have demonstrated an increase from 47% to 74% of the specificity of grey scale prostate US by using power Doppler [21].

Furthermore, Sauvain et al showed that power Doppler US can predict the presence of high-risk PCa. The authors concluded that patients with a normal power Doppler transrectal US have less than 5% risk of aggressive PCa, in cases of prostate specific antigen <10 ng/ml and normal digital rectal examination [22].

Contrast-enhanced ultrasound

CEUS uses intravenous gas-filled microbubbles of similar size with erythrocytes, thus allowing an efficient exploration of the microvessels. CEUS improves the detection rate of PCa up to 86% [23], but can also assist targeted prostate biopsy, increasing the number of positive biopsy cores in comparison with systematic biopsy (11% vs 5%) [24].

In a comparative study between CEUS and MRI, which used as a reference the prostatectomy specimen pathological analysis, sensitivity of 58-69% and specificity of 93-95% of CEUS for the detection of lesions >0.5 ml, similar to MRI [25] was demonstrated. Furthermore, Qi et al [26] observed that transrectal CEUS combined with grey scale US has a detection rate of index lesion of 80.7% in comparison with 66% for contrast-enhanced MRI [27].

A recent study brought in the assessment of new parameters for CEUS – the dispersion and velocity of the US contrast agent, which can improve the detection rate of PCa by a better assessment of prostate vascularization [28]. Another recently developed technique is the three-section contrast-enhanced transrectal US, which showed sensitivity of 92.3%, specificity of 69.2%, and accuracy of 78.1% for the detection of PCa. The higher rate of low grade PCa detected allowed the selection of the patients for active surveillance [29].

Due to the fact that CEUS is highly user-dependent, a new technique has been developed in order to translate the subtle malignancy signs from CEUS recordings into parametric maps, based on a statistical analysis of the wash-in rate. Postema et al observed that the use of CEUS parametric maps to target the prostate biopsy allows decreasing the number of biopsy cores performed with more than 70%, with only 8.5% rate of missed clinically significant cancers [30].

Elastography

Elastography allows the assessment of prostate tissue rigidity and the differentiation between soft and hard areas inside the prostate [31,32]. A harder area is the result of an increased cellularity, microvessels, and collagen deposits [33]. The majority of false positive results are caused by prostatitis and hyperplastic nodules [33].

A prospective unicentric study [34] included 109 patients with PCa assessed by elastography before undergoing radical prostatectomy. The radiologist recorded the suspect areas (right lobe, left lobe, base, middle, apex), which were compared with the prostatectomy specimen pathological analysis (3 mm sections). The elastography identified 439 suspect areas in comparison with the pathological examination, which identified 451 malignant areas. The sensitivity and specificity of elastography for the detection of PCa were 75.4% and 76.7% respectively, with a positive predictive value of 87.8%, negative predictive value of 59%, and accuracy of 76%. For lesions >5mm and Gleason score ≥ 7 , elastography showed a specificity of over 80% [34].

Another possibility is to use elastography for the targeting of prostate biopsy. A meta-analysis of 6 studies, published in 2012, showed a sensitivity of 62% and a specificity of 79% for the diagnosis of PCa using elastography-targeted biopsy, with better results for patients with higher Gleason scores [34-36].

Currently, there are two elastographic techniques used for endorectal prostate assessment: strain elastography (SE) and, more recently, novel shear wave elastography (SWE).

SE requires a manual compressions and decompressions upon the prostate tissue with the endorectal probe. This technique has demonstrated advantages for the de-

tection of PCa, but also for the guidance of prostate biopsy [37]. Brock et al [38] assessed SE in association with MRI-US fusion prostate biopsy in patients with a history of negative biopsy, but persistent suspicion of PCa. The authors observed that elastography significantly increased the prediction of PCa at biopsy (AUC 0.86 vs AUC 0.79). Furthermore, the quantification of SE into a strain index (calculated as the ratio between the region of interest corresponding to a lesion and to a normal area in the prostate) has been shown to correlate with the Gleason score in malignant prostate lesions [37].

In SWE technique the transducer automatically generates the acoustic radiation impulse. This type of elastography has the advantage of providing quantitative information regarding the tissue stiffness and deformation, with no difference in the intra-observer reproducibility [39]. The two studies published so far that compared SWE with sextant prostate biopsy demonstrated high sensitivity and specificity for the diagnosis of PCa (96% and 95% in the first study 90% and 80% in the second study) [40,41].

Multiparametric ultrasound

Multiparametric US is a new concept defined as the combination of CEUS and real-time elastography. The combination of these two techniques was demonstrated to decrease the false-positive results and increase the positive predictive value for the presence of PCa [42].

Brock et al assessed 100 PCa patients before undergoing radical prostatectomy and the suspicious areas were marked into 12 sectors (every prostatic lobe was split in anterior, posterior, base, middle, apex). The results were compared with the pathological result of the prostatectomy specimen by analyzing 4 μ m sections. The positive predictive value of multiparametric US for the detection of PCa was 89.7%. The main advantage of CEUS was to reduce the rate of false positive results of real-time elastography with two-thirds [42].

Another retrospective study demonstrated a detection rate of PCa for multiparametric US of 59.4% (56.5% for elastography, 74.2% for CEUS). These results were obtained using a median of 5 biopsy cores/patient and a median of 3 cores/lesion. The highest detection rate was for patients with prostate volume <40ml (72.2%) and patients older than 70 years (87%) [43].

Ultrasound-MRI-guided prostate biopsy

Two methods have been developed in which ultrasound and mpMRI can be combined in order to assist prostate biopsy: cognitive and fusion biopsy.

MRI-US guided cognitive prostate biopsy

MRI-US guided prostate biopsy implies that the MRI scan of the patient is performed prior to biopsy, with the

identification of suspicious lesions by the radiologist. In order to improve the communication with the urologist, the radiologist can use several methods: delineation of the lesion directly on the MRI images, employment of the sector map of PI-RADS version 2 [7] or localization of the lesion using landmarks like bladder neck, cysts, or hyperplastic nodules [44]. Prostate biopsy is performed with US guidance and the lesion is targeted based on the aforementioned details. Lai et al concluded that, in the setting of a previous negative biopsy, performing MRI-US guided cognitive prostate biopsy and sampling only the suspicious lesions can increase PCa detection rate up to 20.8% in comparison with 14% for a systematic US-guided repeat biopsy [44].

MRI-US fusion guided prostate biopsy

MRI-US fusion guided prostate biopsy is based also on a prior MRI scan. It implies the use of a fusion software that overlaps the MRI of the prostate with the transrectal US in real-time. The lesion is marked on the MRI of the prostate and, after the fusion of the two volumes - MRI and US - the software transposes the lesion mark onto the US, enabling the targeted biopsy. Lacetera et al reported their first experience with MRI-US fusion guided prostate biopsy and showed a clinically significant PCa detection rate of 40% in the setting of repeat biopsy [45].

A recent systematic review by Wegelin et al [46] showed that MRI guided biopsy (any type) is not superior to US guided prostate biopsy in overall cancer detection, but shows improvement in the detection of clinically significant prostate cancer (MRI guided biopsy missed 10%, whereas US guided biopsy missed 21% clinically significant cancers). Furthermore, fusion guided biopsy did not show significant advantages over cognitive biopsy in terms of overall cancer detection ($p=0.11$) or clinically significant prostate cancer detection ($p=0.62$).

MRI-US guided prostate biopsy is a complex technique that faces several limitations in the practical use [47,48]. Apart from the already mentioned MRI limitations, there are also biopsy-related limitations, such as the software registration type or the costs of the procedure.

One of the most important factors to ensure correct localization of the lesion during fusion biopsy is the software registration type. For performing the fusion between the two volumes, elastic systems take into consideration prostate movements and deformation during the insertion of the US probe, whereas rigid systems rely only on internal anatomical markers [49]. Delongchamps et al [50] showed that elastic image fusion was more accurate for cancer detection than rigid image fusion, which performed similarly with cognitive guided biopsy [51].

Incorporation of MRI and MRI-guided prostate biopsy is not without costs. Although Cerantola et al [52] developed a model that suggests that the integration of MRI for assisting the diagnosis and biopsy of prostate cancer is a cost-effective measure even at 20 years after initial diagnosis, the authors admit that the study has some limitations due to the fact that they did not consider the costs related to complications associated with treatment or active surveillance. Furthermore, van de Ven et al [53] showed that almost two thirds of the lesions with a PIRADS score of 5 on MRI were also visible on transrectal US, thus questioning the real need to increase the costs using MRI guided biopsy of these lesions.

Another question that rises is whether systematic biopsy is still needed in addition to MRI guided biopsy. Salami et al [54] showed that performing only MRI targeted biopsy in patients with highly suspicious lesions still misses 3.5% of clinically significant prostate cancers, and 6.2% of the patients that undergo fusion biopsy are upgraded to clinically significant disease at concurrent systematic biopsy [55].

Discussions

It is clear nowadays that conventional transrectal US has reduced its importance in the diagnostic assessment of PCa. But its availability, costs, and the possibility to repeat the examination whenever necessary make it an asset for the urologist. A number of techniques have been developed in order to improve the sensitivity and specificity of grey scale US and they have proven their advantages in terms of PCa detection rate and the guidance of prostate biopsy [15]. Multiparametric MRI has revolutionized the diagnostics of PCa and offered the possibility to perform a true targeted biopsy, but the costs of the investigation, the low volume centers, and the lack of specialists hinder its implementation [12].

A concern that was raised regarding PCa is the problem of overdiagnosis of clinically indolent tumors and underdiagnosis of aggressive PCa [3]. Since the majority of clinically significant PCa is visible using grey scale and new US techniques [2], probably a complex multiparametric US approach would be the best to be offered when patients present with PCa suspicion. In the setting of one negative biopsy and persistent suspicion for PCa, the high accuracy of multiparametric MRI in the identification of PCa [9] makes this investigation the standard for the evaluation of the prostate gland and targeting of the biopsy.

A combination of both techniques might be of help to not miss clinically significant PCa in patients at risk for his malignancy and at least one negative prostate biopsy.

Last, but not least, another issue that was much debated in the last years is whether it is possible to decrease the number of biopsy cores for diagnosis, with the purpose of decreasing the associated morbidity of the procedure. Despite having a high positive and negative predictive value for the presence of PCa, MRI-guided prostate biopsy cannot completely replace systematic biopsy so far [54]. But, as new US techniques develop and multiparametric MRI becomes increasingly used worldwide, the premises are that systematic biopsy will soon be forgotten.

In **conclusion**, although the use of prostate US has decreased after the implementation of MRI, the new developments in US technique have renewed the interest for this imaging method for the assessment of prostate cancer. Power-Doppler, CEUS, multiparametric US, and elastography have demonstrated an increase in the diagnosis of significant PCa. More complex techniques such as MRI-US guided biopsy increase even more the accuracy of prostate biopsy, but still face some limitations in terms of technical issues and costs. A thorough reevaluation of the selection criteria of the patients is required to assess which patients would benefit from multiparametric US, which would benefit from mpMRI or the combination of both to assist prostate biopsy in order to ensure the balance between overdiagnosis and underdiagnosis of PCa.

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