Acta Biomed 2020; Vol. 91, Supplement 10: e2020006 10.23750/abm.v91i10-S.10273

Original article

Software-assisted US/MRI fusion-targeted biopsy for prostate cancer

Salvatore Alessio Angileri[1], Letizia Di Meglio[2], Mario Petrillo[3], Antonio Arrichiello[2], Marco Pandolfi[1], Giovanni Maria Rodà[2], Giuseppe Granata[2], Anna Maria Ierardi[1], Daniela Donat[4], Aldo Paolucci[5], Gianpaolo Carrafiello[1-6]

[1]Operative Unit of Radiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [2]Postgraduation School in Radiodiagnostics, Università degli Studi di Milano, Milan, Italy; [3]ASST Rhodense, Garbagnate Hospital, Milan, Italy, Garbagnate Milanese, Milan, Italy; [4]Clinical Center od Vojvodina, Center for Radiology, Serbia, Novi Sad, Hajduk Veljkova 1; [5]Operative Unit of Neuroradiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; [6]Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Abstract. *Background*: Prostate cancer is the first cancer diagnosis in men. European Association of Urology (EAU) Guidelines for Prostate Cancer underline the importance of screening, performed through PSA testing on all men with more than 50 years of age and before on men with risk factors. The diagnosis is still histopathologic, and it is done on the basis of the findings on biopsy samples. *Materials and Methods***:** Fusion biopsy is a relatively new technique that allows the operator to perform the biopsies in office instead of the MRI gantry, without losing the detection capability of MRI. The T2-wighted images obtained during a previous mpMRI are merged with the real-time ones of the TRUS. *Results***:** Fusion biopsy in comparison with the systematic standard biopsy has a better detection rate of clinically significant cancers and of any cancers. *Conclusion***:** EAU 2020 guidelines still do offer a list of indications of when the biopsy should be performed, but it still appeared to be overperformed. The aim of our study is to underline how, in accordance with the recent literature result, fusion biopsy has showed a better detection rate of any cancer and clinically significant disease with a reduced numbers of samplings, and no substantial difference between the multiple software. (www.actabiomedica.it)

Key words: Prostate biopsy, Prostate cancer, Fusion Biopsy, TRUS

Background

Prostate cancer is the first cancer diagnosis in men representing the 20% of all cancer diagnosis in men in the 2019 in the United States of America, and is the second death cause for cancer in men representing the 20% of all the deaths for cancer in the United States of America in 2019 (1).

Thanks to the improvement in the diagnosis and to the screening campaigns, is it possible now to ensure a prompt diagnosis to ensure the most adequate and timely treatment for the patient.

Clinical suspect of prostate cancer normally comes from a positive family anamnesis for prostatic cancer, suspicious findings during a digital rectal exploration (DRE) and from an increment of the value of prostate specific antigen (PSA). The recent introduction of the multiparametric (mpMRI) permits a non-invasive evaluation of prostatic lesions.

The diagnosis is still histopathologic, and it is done on the basis of the findings on biopsy samples, specimen from transurethral resection of prostate (TURP) and on prostates obtained after radical prostatectomy.

Prostate biopsy has changed over time and can be targeted and non-targeted and can be performed with an Ultra Sound (US) guidance, a Magnetic Resonance Imaging (MRI) guidance (MRI-Guided In-Bore Biopsy) or through a fusion of the previous techniques that can be cognitive or provided by a software.

As recommended in the EAU 2020 guidelines prostate lesions samples should be evaluated through a score system, the International Society of Urological Pathology (ISUP) 2014 system, in order to estimate the cancer aggressiveness (2,3).

Materials and Methods

Screening

In accordance with the latest version of the EAU Guidelines for Prostate Cancer PSA testing should be used to screen all men with more than 50 years of age, men with more than 45 years of age and a positive family history of prostate cancer or an African descent and men with more than 40 years of age if carrying BRCA2 mutations. PSA testing should be done after a detailed counselling of the beneficial effects and potential risks (4).

The EAU guidelines 2020 underlines also the absence of a PSA threshold so it recommends, in order to minimize the number of prostate biopsies, that are still overperformed, to calculate the risk and to perform imaging investigations in those patients with a PSA level between 2-10 mg/ml and a negative DRE (2,5,6).

It also specifies that mpMRI should not be used as a screening tool, instead the usage of the mpMRI imaging is strongly recommended prebiopsy in the naïve patients and in patients with a prior negative prostate biopsy. MpMRI should be performed and interpreted in accordance with PI-RADS guidelines (7,8).

Prostate biopsy

The biopsy could be targeted and non-targeted, the targeted ones require a previous imaging to identify the location of the lesion.

The traditional approach of prostate biopsies is the systematic non-targeted TRUS. The technique consists in collecting bilateral systematic samplings from apex to base of the prostatic gland, the cores collected varies according to the volume of the prostate, going from 8 cores in 30 ml prostates to 10-12 in larger glands. The great limitation of this technique is represented by the lack of sampling of the central zone and by the risk of non-recognition of a prostatic neoplasia, because the samplings normally are collected form the peripheral zone of the gland (4,9,10).

US guided biopsies can be performed with both a trans rectal (TR) and a trans perineal (TP) approach. Recent studies have demonstrated a substantial equality between the two techniques, except for the sepsis risk that appears to be reduced in the TP approach meanwhile the pain is minor in the TR approach (2).

One of the advantages of the US guided biopsies is to be performed in office. TRUS still lacks on the evaluation of apical and anterior lesions, the limitation of the US technique is the worse definition in the localization of the lesion.

Due to the better detection of MRI in localizing the lesions, MRI can be used as guidance in the prostate biopsy, of course, the limitation of the technique is represented by the costs and by the necessity of performing the biopsy in outside the office ambient, in the RMI gantry (11,12).

Another way of performing the biopsy is represented by the cognitive biopsy, in this approach the operator in accordance with the findings of the mpMRI locates the lesion and performs a targeted biopsy, the great limitation of this technique is clearly the operator-dependency.

In this context fusion biopsy is a relatively new method, that allows to synthetize the capability of mpMRI in detecting the lesion with the real-time approach of US techniques.

Fusion biopsy is a technique that allows the operator to perform the biopsies in office instead of the MRI gantry, without losing the detection capability of MRI. This might represent an important tool in high-flow centers with short availability of time and no dedicated MRI for biopsy procedures. The T2-wighted images obtained during a previous mpMRI are merged with the real-time ones of the TRUS.

The biopsy is performed with US guidance and the approach can be both Trans-Rectal and Trans-Perineal, in accordance with the capability of synthesis

of the used system (13). The US approach permits to have a real time visualization and once the lesion is located via US the software merges the US images with the mpMRI ones (8,11).

Fusion technique

In order to correctly assess the characteristics of prostate lesions, mpMRI should be performed through multiple sequences, including anatomic sequences, like a multiplane T2 and at least two functional sequences, normally a diffusion weighted imaging (DWI) and a dynamic contrast enhancement (DCE) (14).

There is many different software to perform the fusion biopsy, they vary in the tracking mechanism, in the biopsy route and in the imaging fusion technique.

Although they present differences, all the available platforms follow the same steps. The first step consists in performing a mpMRI and locating the target lesion. Once the suspicious lesions are assessed, the target lesion and the prostate undergo a process of segmentation on mpMRI and the data are uploaded in the US system.

The image registration is performed, the method might require a delimitation of the prostate boundaries or the identification of landmarks, in order to overcame the deformation of the prostate on the US. Subsequently the prostate undergo a US segmentation thought the acquisition via a sweep of the US probe of bidimensional (2D) images and the three-dimensional (3D) US volume is obtained.

Once the prostate evaluation via US is done, the data acquired by US and mpMRI are fused together.

The fusion process has the aim of aligned images obtained by US and mpMRI. This procedure differs between the several fusion systems and require the identification of the boundaries and the region of interest (ROI) on both the US and the mpMRI images and the eventual transformation of the latter images. The transformation process can be rigid or elastic.

In the rigid registration the images cannot be deformed, they can be translated and rotated. This system allows a preservation of the anatomy of the prostate and lesion's location.

In the elastic registration the images can be translated and rotated and in addition the operator can alter the image scale deform it, in order to match perfectly the US images and the mpMRI ones. This second form of registration might alter the anatomy of the gland.

To optimize the location of the targeted lesion the majority of software are now equipped with both registrations to allow the operator to obtain a more accurate fusion of the US and mpMRI images and location of the targeted lesion.

The presentation of the fused images varies according to the system used, images can be showed side-by-side or superimposed.

Before performing the biopsy, the ROI should be localized on the real-time US images, the software through a process of mapping, tracking and navigation allows the operator to optimize the visualization of the ROI. Mapping consist in assess and register the likely location of the biopsy cores on the mpMRI images, while navigation is the acquisition of real-time images to improve the targeting of the lesion. Tracking eventually represents the ability of visualizing the US probe and the needle in a 3D volume during the procedure. This process optimizes the spatial definition of the ROI, ensuring a better targeted biopsy. Tracking differs between the various software, it can be generated by an electromagnetic field, as in the Electromagnetic Tracking, by angle sensor as in the Smart Robotic Arms Tracking or by the US acquisition as in the Image-Base Software Tracking (11,15,16).

Fusion Software

Artemis (Eigen, Grass Valley, CA) is a platform that uses a mechanical tracking system. The workflow follows the steps previously reported, a pre-biopsy mpMRI, targeting of the prostatic lesion, segmentation of the gland, registration of the images, mapping, navigation and tracking of the lesion. The peculiarity of Artemis is represented by the tracking system that is performed thought angle sensing encoded joints located on a mechanical robotic arm positioned on the operating table, which held the US probe. The probe can be rotated with only 2 degrees of freedom. The fixed robotic arm corrects the human error and arise the accuracy in targeting the lesion. The fusion process is semiautomatic and merges the mpMRI data with the US ones, creating a 3D model. The platform allows

to collect cores with an interval of 3 mm, to increase the accuracy of the procedure.

The Artemis offers the operator the possibility of registering and tracking the biopsy's site, permitting the operator to re-perform the biopsy in the same site. The fixed arm permits to correct the errors related with the unsteadiness of the human and.

BiopSee platform (Pi Medical, Greece), as Artemis, used a mechanical tracking system, operating through mechanical fixation device with two built-in tracking encores, located over the operating table. As in the Artemis platform the TRUS in placed in the fixation device and can me moved only by rotation with 2 degrees of freedom. The peculiarity of BiopSee is to use only the TP approach.

The software design is modular with each procedure step mapped in a separate software module. The workflow of the process is the same as the one preformed in Artemis. Biopsee only allows a rigid registration system.

Virtual Navigator (Esaote, Genoa, Italy) works following the same fusion steps as all other platforms described. Its application has involved majorly other interventional procedures. The platform offers a rigid registration and the mpMRI images are overlaid on the US ones.

The **UroNav** platform (Invivo/Philips, USA): developed by the National Institutes of Health (NIH).

The process requires a pre-biopsy mpMRI. The radiologists locate the lesion and proceed to the segmentation of the prostate and the targeted lesion, those data and information are sent to the UroNaV software. The platform works through an electromagnetic tracking, so the field generator is placed to the operating table and positioned on the pelvis of the patient, who is laid on the operating table. This form of tracking gives the operator the possibility to manipulate the US probe with multiple degrees of freedom. In addition, the UroNav system offers both rigid and elastic registrations in order to allow a better alignment of the US and MRI images. The fused images are presented both side-by-side and overlaid. To reach the ROI the operator uses a freehand US probe, permitting the evaluation of multiple different approach and visualization angles. As reported in literature the UroNav system has a high level of accuracy and with a reported margin of error in registration and tracking of 2-3 mm.49 The latest versions of UroNav system offers both TR and TP approaches. The limitation of the platform is represented by the unsteadiness of free-hand approach. UroNav like Artemis has the possibility of register the site of the biopsy, in order to allow the operator to eventually re-biopsy in the same zone (Fig. 1).

Urostation (Koelis, France) is an Image-based tracking Platform. The workflow is the same as the other systems. Urostation differs from the other platforms by the absence of an external tracking hardware, due to the technology that allows to perform the tracking only on the base of the 3D TRUS image.

A panoramic 3D reference volume image of the prostate is constructed after the acquisition of three 3D TRUS images from different views. A manual segmentation of the mpMRI is performed on the 3D reference volume, the images are registered to reduce the errors related to the US probe deformation. During the procedure the operator uses both 2D real-time TRUS images and 3D TRUS images, the first ones are used as a guide to locate, once the targeted lesion is located the 3D TRUS is used to acquire positional information. Eventually the biopsy needle is positioned and a 3D TRUS image is acquired retrospectively to locate the biopsy site.

Complications

The most frequent complication following the TRUS is represented by haematospermia, other complications related with the procedure are hematuria, rectal bleeding, urinary tract infections, fever and urinary retention. A major complication is sepsis, it could represent a life-threatening condition that requires hospitalization, due to the presence of a rectal bacterial flora. Recent studies have demonstrated a substantial equality between the two techniques, except for the sepsis risk that appears to be reduced in the TP approach meanwhile the pain is minor in the TR approach. TP approach appeared to be associated with a reduced risk of injury to the Santorini plexus, related with biopsy of the anterior area of the prostate (17-20).

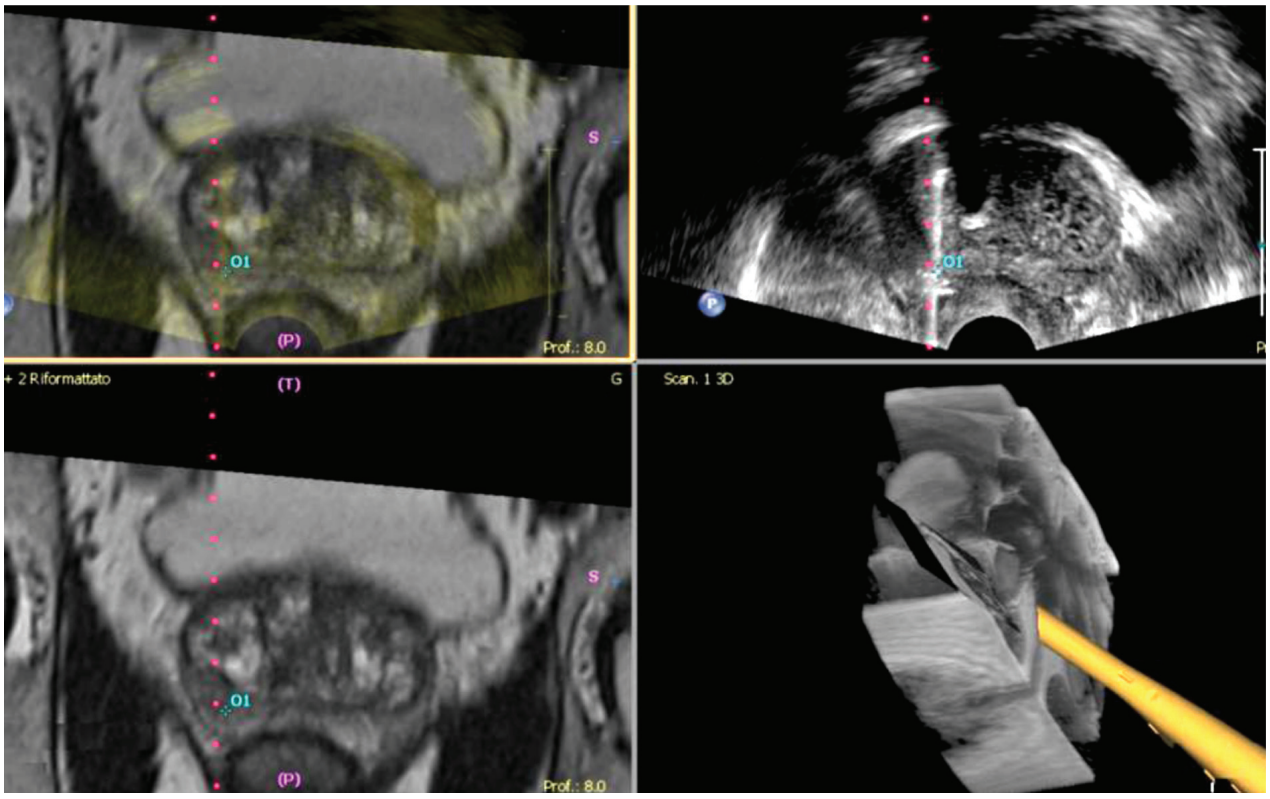

Figure 1. A 70-year-old man with a PSA value of 4.5 ng/mL. MpMRI was performed, showing a right peripheral lesion located in the intermediate zone evaluated in accordance with the PI-RADS v2.1 guidelines as PI-RADS 3. Images of the fusion biopsy performed with the UroNav platform (Invivo/Philips, USA) with a TR approach. MpMRI images overlaid on the TRUS images. [A] Real-time TRUS images showing the needle (16G) in the targeted lesion. [B] T2-weighted axial view MpMRI images showing a hypointense area in the right peripheral zone (01).[C] 3D reconstruction of the fused images showing the position of the rectal probe during the procedure. [D] Targeted biopsy demonstrated a 4+4 Gleason score cancer.

Results

As Valerio et al outlined in their review made in the 2015 fusion biopsy in comparison with the systematic standard biopsy has a better detection rate of clinically significant cancers and of any cancers. The results presented showed a median detection of clinically significant disease of 23.6% (range: 4.8–52%) for standard systematic biopsy versus the 33.3% (range: 13.2–50%) median detection rate of the fusion targeted biopsy. Thee review also underlined the substantial equality of the outcomes of the different software used in the different studies. The clinically significant disease was indicated as the presence of a Gleason pattern ≥ 4 in the biopsy samples (21). Standard systematic biopsy showed a median detection rate of in identifying the presence of any cancer 43.4% (range: 14.3–59%) while fusion biopsy had a median rate of 50.5% (range: 23.7–82.1%) (22). As Martorana et al underlined in their revision in 2010 the TP approach allows a major accuracy in sampling the anterior part of the gland, which is poorly sampled in the traditional TR approach, resulting in a greater detection rate of clinically relevant cancers located in the anterior area of the gland. No significant difference was found between the TR and the TP approaches in targeting the lesion located in the other portions of the prostate (19). The infectious complications related to the procedure appeared to be reduced in the TP as for the risk of injury to the Santorini plexus, associated with biopsy of the anterior area of the prostate. The main disadvantage of the TP approach is represented by a higher pain for the patient that might require a sedation(19,23).

As demonstrated by Wegelin et al in the review of the 2017, fusion target biopsy and in-bore MRI target biopsy have similar results in detecting both clinically significant diseases and any cancers (24).

In addition, as reported by Kayano et al in their retrospective study of the 2019 fusion target biopsy appeared to be associated with a lower rate of Gleason upgrading if compared to the standard TRUS biopsy, demonstrating the possibility of improving prostate cancer characterization at biopsy (25).

Conclusion

The EAU 2020 guidelines still do offer a list of indications of when the biopsy should be performed, but it still appeared to be overperformed (2). The literature results have showed better outcomes in detection rate of any cancer and clinically significant disease of the fusion biopsy in comparison with the standard systematic biopsy. Those results are obtained with a reduced numbers of samplings (22). Moreover, the studies have showed no substantial difference between the multiple software. Our aim is to underline the benefits of the fusion biopsy as the better detection rate of clinically significant disease compared with the standard systematic US guided biopsy associated with the possibility of performing the procedure in-office. Of course, this procedure in not free of limitations, the main one is the high cost of the fusion software. TRUS is still the more performed approach, in particular among the fusion biopsies, the TP approach is offered only by few software even though the benefits of this technique, in reducing the infectious complications and the hospitalization have been outlined in recent literature (19).

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent to the CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2019. CA. Cancer J. Clin. 69, 7–34 (2019).
2. EAU. EAU 2020 Guidelines for Prostate Cancer. https://uroweb.org/guideline/prostate-cancer/ (2020).
3. Epstein, J. I. et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur. Urol. 69, 428–435 (2016).
4. Djavan, B. & Margreiter, M. Biopsy standards for detection of prostate cancer. World J. Urol. 25, 11–17 (2007).
5. Roobol, M. J. et al. A Risk-Based Strategy Improves Prostate-Specific Antigen-Driven Detection of Prostate Cancer. Eur. Urol. 57, 79–85 (2010).
6. Pesapane, F. et al. The prostate cancer focal therapy. Gland Surgery vol. 7 89–102 (2018).
7. PI-RADS ® v2.1 PI-RADS ® Prostate Imaging-Reporting and Data System 2019 Version 2.1 PI-RADS ® Prostate Imaging-Reporting and Data System 2019 Version 2.1.
8. Streicher, J., Meyerson, B. L., Karivedu, V. & Sidana, A. A review of optimal prostate biopsy: indications and techniques. Ther. Adv. Urol. 11, 175628721987007 (2019).
9. Eichler, K. et al. Diagnostic Value of Systematic Biopsy Methods in the Investigation of Prostate Cancer: A Systematic Review. J. Urol. 175, 1605–1612 (2006).
10. Shariat, S. F. & Roehrborn, C. G. Using biopsy to detect prostate cancer. Rev. Urol. 10, 262–80 (2008).
11. Verma, S. et al. The current state of MR imaging-targeted biopsy techniques for detection of prostate cancer. Radiology vol. 285 343–356 (2017).
12. Pesapane, F. et al. Intravoxel Incoherent Motion (IVIM) Diffusion Weighted Imaging (DWI) in the Periferic Prostate Cancer Detection and Stratification. Med. Oncol. 34, 1–9 (2017).
13. Guo, L. H. et al. Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. Sci. Rep. 5, 1–10 (2015).
14. Bastian-Jordan, M. Magnetic resonance imaging of the prostate and targeted biopsy, Comparison of PIRADS and Gleason grading. J. Med. Imaging Radiat. Oncol. 62, 183–187 (2018).
15. Michael Kongnyuy, M.S, Arvin K. George, M.D, Ardeshir R. Rastinehad, D.O, and Peter A. Pinto, M. . Magnetic Resonance Imaging-Ultrasound Fusion-Guided Prostate Biopsy: Review of Technology, Techniques, and Outcomes. Curr. Urol. Rep. 176, 139–148 (2017).
16. Schütz, V. et al. Multiparametric MRI and MRI/TRUS Fusion Guided Biopsy for the Diagnosis of Prostate Cancer. Adv. Exp. Med. Biol. 1096, 87–98 (2018).
17. Borkowetz, A. et al. Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer. BJU Int. 116, 873–879 (2015).
18. Borghesi, M. et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy [figure presented]. European Urology vol. 71 353–365 (2017).

19. Martorana, E. et al. Prostate MRI and transperineal TRUS/MRI fusion biopsy for prostate cancer detection: Clinical practice updates. Turkish J. Urol. 45, 237–244 (2019).
20. Ierardi, A. M. et al. Bleeding after prostatectomy: Endovascular management. Gland Surg. 8, 108–114 (2019).
21. Martorana, E. et al. Lesion volume predicts prostate cancer risk and aggressiveness: validation of its value alone and matched with prostate imaging reporting and data system score. BJU Int. 120, 92–103 (2017).
22. Valerio, M. et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: A systematic review. Eur. Urol. 68, 8–19 (2015).
23. Loeb, S. et al. Systematic review of complications of prostate biopsy. Eur. Urol. 64, 876–892 (2013).
24. Wegelin, O. et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? Eur. Urol. 71, 517–531 (2017).
25. Kayano, P. P. et al. Comparison of Gleason upgrading rates in transrectal ultrasound systematic random biopsies versus US-MRI fusion biopsies for prostate cancer. Int. Braz J Urol 44, 1106–1113 (2018).

Received: 19 July 2020
Accepted: 22 October 2020
Correspondence:
Antonio Arrichiello MD,
Postgraduation School in Radiodiagnostics,
Università degli Studi di Milano, Milan, Italy
Via Festa del Perdono 7, 20122, Milan, Italy
E-mail: arrichielloantonio@gmail.com