Prostate MRI and transperineal TRUS/MRI fusion biopsy for prostate cancer detection: clinical practice updates

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ABSTRACT

This narrative review summarizes the current knowledge about multiparametric and biparametric magnetic resonance imaging of the prostate. This is provided from both a radiological and a urological point of view analyzing the technical aspects of fusion-targeted biopsy using the transperineal approach. We report practical considerations concerning pure cognitive and software-assisted settings, discuss the principal transperineal fusion software now available, and debate the pros and cons of choosing one approach over the other.

Keywords: Biparametric MRI; cancer; fusion biopsy; prostate.

Introduction

Prostate cancer (PCa) is the most common tumor and the second highest cause of death in the male population.[1] A prostate biopsy is considered the gold standard for PCa diagnosis. This procedure has considerably changed over time and the 12-core ultrasound-guided sampling schema[2] is considered the gold standard for biopsy-naïve patients. However, ultrasound (US) guiding is largely criticized for its low sensitivity in the detection of suspected PCa lesions (SL). This results in a possible over-detection of indolent tumors (iPCas) and an under-detection of significant cancers (sPCas).[3,4] Noguchi et al.[5] underlined the lack of tumor significance prediction by US-guided biopsy, showing 40% of tumor downgrading as compared to definitive surgical specimens.

Recently, multiparametric Magnetic Resonance Imaging (mpMRI) has been proposed as a promising solution to improve sPCa detection. In-gantry biopsy (obtaining tissue samples with direct MR imaging guidance while the patient is in the MRI gantry) was the first method proposed for MRI-targeted biopsies.[6] This approach is now replaced by the most widespread US/MRI fusion-targeted biopsy that has proven to be advantageous over standard practice for both biopsy-naïve and previous negative biopsy patients in large prospective studies providing level 1b evidence of cancer.[7]

The US/MRI fusion was initially performed in a cognitively approach. Soon, systems providing a computerized US/MRI fusion process were introduced in clinical practice with the aim to optimize the fusion process. A major difference between these systems concerns the transrectal or transperineal (TP) access to the gland.[8]

In this narrative review, we summarize the current knowledge on prostate MRI and US/MRI fusion-targeted biopsy using the TP approach, report technical considerations, and discuss the pros and cons of choosing one approach over the other.

Magnetic Resonance Imaging of the Prostate

Patient preparation

Data regarding the patient's age, clinical history, familiarity with PCa, previous prostate biopsies, and current total and ratio of PSA values should be collected before the examination and included in the final report.

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The patient should be informed in advance about methods, duration, and rationale of the examination. All images should be obtained immediately after administering an intramuscular injection of 1 mg of butylscopolamine (Buscopan; Boehringer Ingelheim GmbH, Germany), with the aim to reduce peristalsis of the rectum, which improves the image quality. Moreover, anesthetic support may be required in patients with anxiety and claustrophobia.

Multiparametric MRI

Prostate imaging interpretation is based on prostate imaging reporting and data system version 2 (PIRADS v2) guidelines.[9] MpMRI includes T2-weighted (T2W), diffusion-weighted (DW). and dynamic contrast-enhanced (DCE) MRI sequences. In PIRADS v2, spectroscopy was omitted and DCE MRI had a minor role as compared to the first version. DW-MRI is considered the predominant sequence for detection of a lesion in the peripheral zone (PZ) while T2W sequences are more relevant for detection of lesions in the transitional zone (TZ).

To minimize interpretation errors, images should be analyzed by a radiologist with at least 5 years of experience in interpreting prostate mpMRI scans. The radiologist should assign a score to all SL identified scans basing on PIRADS v2 criteria[9,10], which identifies five categories of mpMRI-detected lesions. Although lesions with a score of 4 and 5 should always be sampled, there is still no consensus about the management of lesions with a PIRADS score of 3. This issue represents one of the most important ambiguities and limitations of this system.[11,12]

Different authors have tried to solve this dilemma. Liddell et al.[13] concluded that prostate lesions characterized with a PIRADS score of 3 are associated with a low likelihood of sPCa and therefore should be only monitored, not treated. In contrast, Thompson et al.[14] reported a 26% PCa overall detection rate in such lesions, among which 38% were moderate- or high-risk lesions.

Kaufmann et al.[15] introduced the prostate cancer antigen 3 (PCA3) as a clinical discriminator to indicate which PIRADS 3 lesions are worthy of biopsy and proposed a urinary PCA3 cut-off of 35 to avoid potential unnecessary biopsies. Despite these efforts, there is still no universally accepted discriminator that provides the date of performing and the decision whether to do a targeted biopsy of PIRADS 3 lesions. The discriminators existing are mainly based on the patient's individual risk profile.

Biparametric MRI

Biparametric MRI imaging (bpMRI) (which excluded the DCE-MRI sequences and combined the axial fat suppression with T1W, T2W, and DW MRI series) has been proposed as an alternative to mpMRI for PCa detection and localization.[16-22] BpMRI demonstrated similar accuracy to mpMRI, with a concomitant reduction of overall costs and procedural time.[23-26]

According to the criteria and lexicon of the PIRADS v2 guidelines[11] and based on the results reported in the literature and the EMA's Pharmacovigilance Risk Assessment Committee recommendations (which suspended the marketing authorization for four linear gadolinium contrast agents for intravenous injections that caused small amounts of gadolinium to deposit in the brain), we recently proposed a simplified PIRADS (S-PIRADS) for the risk assessment and management (biopsy or active surveillance) of suspicious PCa.

The S-PIRADS[23] is based on a 3T MRI unit without an endorectal coil. The bpMRI protocol adopted a triplanar T2W and axial DW sequence, using 4b values from 0 to 2000 s/mm^2 and calculation of ADC maps.

S-PIRADS considers four lesions' categories, as shown below:

- Category 1 (corresponds to category 1 PIRADS v2) includes normal prostate gland with no abnormalities present (follow-up by PSA);
- Category 2 (corresponds to category 2 PIRADS v2) includes focal, rounded, lenticular or irregular mild/moderately or markedly hypointensity lesions without a correlated restriction of diffusion on DWI/ADC (follow-up by PSA and bpMRI eventually within 2 years);
- Category 3 (corresponds to category 3 PIRADS v2) includes focal, rounded, lenticular or irregular areas with heterogeneous or homogeneous, mild or moderately markedly hypointensity on T2W, hyperintense on DW MRI at a high b value and moderately hypointense on ADC map; the lesions with volume <0.5 cc (category 3a) should be followed-up by PSA and bpMRI within 1 year, while lesions with volume >0.5 cc (category 3b) should be biopsied;
- Category 4 (corresponds to category 4 and 5 PIRADS v2) includes intraglandular and extraglandular, focal, rounded, lenticular, or irregular areas with heterogeneous or homogeneous mild/moderately or markedly hypointensity on T2W, hyperintense on DW imaging with high b value, and markedly hypointense on ADC map; such lesions should always be sampled.

We herein report the main characteristics of S-PIRADS:

1. DW MRI is the dominant sequence for detection of lesions in both the PZ and TZ; lesions that are hyperintense on DWI with high b value and moderately or markedly hypointense on ADC map are confirmed and accurately localized as hypointense areas on T2W. We recommend standardization of image interpretation based on the detection of the lesion pattern first on DW/ADC map and then on T2W map.
2. PIRADS v2 score 3 (equivocal for sPCa) lesions are considered heterogeneous or homogeneous mild/moderately or markedly hypointensity areas on T2W, hyperintense on DW with high b value and moderately hypointense on ADC map; for these lesions, we measure the general volume on DWI with high b value using the standard ellipsoidal formula (width×height×length×0.52); alternatively we use

software with three-dimensional (3D) reconstruction.
3. Cutoff volume for score 3 lesions is 0.5 cc, with lesions having volume <0.5 cc or >0.5 cc that are categorized as 3a or 3b, respectively.
4. A total of 41 sectors are present on the map of the prostate; we added these to the current 39-sector maps of the PI-RADS v2 with two additional segments (right and left) for the median lobe.

Why choose the transperineal approach?

The first needle prostate biopsy was conducted by Barringer in 1922 via the perineum using a screw tip needle.[27] Subsequently, this approach was abandoned and replaced by the more common transrectal route. Recently, the TP approach is gaining a following because of its potential advantages as explained below. In the last 20 years, a progressive increase in infectious complications after the transrectal biopsy has been observed. The rate of re-hospitalization rate for infection has increased from 1% in 1996 to over 4% in 2005.[28,29] Likewise, a resistance of above 22% by rectal coliform bacteria to fluoroquinolones has been reported.[30,31] In contrast, the TP approach is considered a sterile biopsy with a substantially reduced risk of infection[32] and decreased hospitalization rate for urosepsis.[8,33-35]

Moreover, the biopsy needle is directed along the longitudinal axis of the prostate, which makes this approach more accurate for sampling the anterior part of the gland, the prostate base and the far lateral lesion (especially for large volume prostates), resulting in a greater PCa detection rate.[36-38] The longitudinal direction of the needle is potentially safer because it presents a low risk of injury to the Santorini plexus injury when the anterior zone is sampled.

Rectal bleeding was found to be a common complication of transrectal approach with a varying rate of 1.3%–45%[39] when the same cases requiring transfusion were described (Clavien-Dindo III). In the TP approach, the occurrence of this complication is impossible because the needle trajectory is always parallel to the anterior wall of the rectum. Consequently, this approach can be safely used in patients under treatment with anticoagulants or those suffering from rectal diseases.

Conversely, the main disadvantages of the TP approach are represented by a greater patient discomfort that could require moderate sedation, because of greater sensitivity of the percutaneous puncture and a longer learning curve for the operator.

Biopsy techniques

Transperineal cognitive US/MRI fusion-targeted biopsy

The term *"cognitive"* indicates that the overlapping of US and MRI scans is performed exclusively by the operator's brain. In other words, the surgeon performs pre-biopsy planning by studying the MRI examination (identification of the SL), establishing the location of suspicious areas (i.e.,base, mid or apex, left or right lobe of the gland, peripheral or TZ) and correlates them with the shape and size of the prostate. Alternatively, the SL location can be reported on the appropriate 39-sector PIRADS v2 map[9,10] to facilitate the identification of the glandular site in order to direct the biopsy. This is particularly useful when more than one SL is detected within the gland and/or multiple biopsy procedures are performed in a single session, as it reduces the surgeon's effort and eliminates the time related to the pre-biopsy re-evaluation of the MRI findings.

Before the biopsy, the patient is placed in the lithotomic position to gain optimal access to the perineum. To facilitate the "cognitive" transposition of MRI findings in real-time US images, a preliminary transrectal ultrasound scan (TRUS) should be performed. This step allows the clinician to assess the morphology of the gland and to look for the presence of any hypoechoic area close to the mpMRI SL.

Alternatively, the operator should check for any US landmark superimposable to those identified at MRI examination (i.e., apex, maximum transversal diameter of the gland, seminal vesicles, urethra, bladder floor, middle lobe, glandular calcifications, retention cysts) to define the precise location of the site in which to perform the biopsy. Finally, the biopsy needle is inserted via a single hole in the midline of the perineum, 1.5 cm from the anus[8] and passed through the prostatic apex along a longitudinal trajectory until the target area is reached.

All the biopsy cores should be collected using a disposable biopsy needle of 18 G x 16 cm mounted on a reusable biopsy gun. We recommend performing at least three samples for each SL to reduce the localization error due to "cognitive" data transposition. All samples should be collected in blocks, named according to the sampling area, and sent separately for histopathological examination.

Different authors investigated the role of cognitive MRI-targeted biopsy in naive patients[40] and in patients with previously negative prostate biopsies.[41,42] They reported superiority of this method compared to the systematic prostate biopsy and showed overlapping results to those of software-assisted US/MRI fusion methods.

Despite these results, cognitive biopsy has some limitations, which are as follows: a) the lack of a standardization of the technique, b) the procedure depends on the skill of the surgeon in translating the SL identified at MRI examination to the images visualized at the US real-time evaluation, c) the detection rate strictly depends on the ability of the operator to navigate free-hand within the prostate tissue until the needle reaches the target area. The advantages of this approach are that it is less expensive and there is no requirement to learn the fusion software.

Software-assisted US/MRI fusion-targeted biopsy

The major limitations of in-gantry biopsy (tissue samples obtained under direct visualization of the MRI SL) are its restricted avail-

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ability, long duration of the procedure, absence of real-time feedback, the complexity of the operator learning curve, requirement of needles compatible with MRI, and costs of using MRI resources for the biopsy. Moreover, this procedure is not compatible with a urologist's scope because the biopsy is performed in the MRI unit of the radiology department rather than in an office setting, which presents logistical and economic disadvantages for urologists.[43]

For the above reasons, software-assisted US/MRI fusion-targeted biopsy has currently become the most widespread method to perform fusion-targeted biopsy.[44] Each of these systems uses the principle of overlapping MRI images with real-time US images for the purpose of allowing the sampling of SL using a US guide. This approach has a triple advantage: a) it exploits the high sensitivity and specificity of mpMRI in the detection of SL; b) it provides the ease of use of real-time US guidance; c) it guaratees the possibility to perform a targeted biopsy in an office setting. In this way, the sampling of the gland is obtained under US guidance, but the software indicates the site of the MRI SL to the operator on which the biopsy is to be directed.

The main disadvantage of this method is the high cost of the fusion software. This currently represents the main limitation against the complete spread of this technology in all urological centers. To our knowledge, only a few systems that allow US/MRI fusion biopsies by the TP approach are available on the market.

Esaote MyLab Twice system® (Esaote, Genoa, Italy): Transperineal Freehand US/MRI fusion target biopsy

This platform is a US system that enables the import of MRI data sets. This is achieved by inserting a CD-ROM with the mpMRI (or bpMRI) exam in the CD player, clicking the icon "IMPORT by CD", and then clicking the icon "IMPORT ALL series". After the sequences are imported, it is possible to select one or more sequences (e.g., axial T2 sequence and DWI) on which the clinician can identify and locate the SL. The ACQUIRE button allows the overlapping of both. Once the SL has been identified (hypointense in the T2W sequence and hyperintense in the DWI sequence), the TARGET button allows the the operator to place an ROI on the identified area. The SAVE A CONFIGURATION function allows the saving those MRI sequences that are demarcated by the ROIs. By convention, the virtual target is positioned in the most apical (proximal) portion of the suspected lesion to ensure that the needle carriage can advance into the area to be biopsied. This is a peculiarity of the TP approach, wherein the needle always advances with the same orientation in the apical-basal direction.

The ONE PLANE button allows visualization of the MRI sequences with marked SL in the left part of the monitor. In the right part, the US images appear once the transrectal probe is put in place. These steps can be performed before the arrival of the patient in the office, thereby shortening the procedure time.

With the aid of an Esaote® TRT33 Bi-Plane endocavitary probe, US images are displayed and a local anesthetic is applied (4 cc of 2% mepivacaine via 21 G needle) with access on the median raphe approximately 1.5 cm from the anal orifice. The anesthetic is injected behind the apex of the prostate and delivered in a "horseshoe" shape around the side of the apex.

The virtual navigator system proceeds with fusing the US/MRI images with continuous real-time control over the overlap of the images. To perform this step, it is advisable to select the MRI sequence where the greatest axial diameter of the gland appears. By translating the US probe in a caudocranial direction, the larger US diameter of the gland is determined. At this moment, the AQUIRE button displays the fused US/MRI images.

Real-time fusion is achieved through continuous communication between the US probe equipped with a tracking device and a magnet that is placed on the patient's abdomen to verify the real-time, the spatial coordinates of the biopsy needle and the virtual targets (suspect areas) to be biopsied. After successful fusion is achieved, the screen can be set to display one fused image representing real-time US/MRI overlapping.

Additionally, the amount of transparency can be changed manually to allow the user to choose the intensity of the US or MR images displayed. Thus, one can achieve simultaneous visualization of the data obtained by the two sources or alternatively see either the US or MR image.

The FINE-TUNING function allows restoration of the fused US/MRI images when the fusion quality is lost due to possible movements of the patient. An 18 G, 20 cm biopsy needle is introduced at the access point in the anesthetized area and extended to the virtual targets planned for MRI using axial US scanning. Biparametric MRI and US/MRI transperineal fusion biopsy is showed in Figure 1. This approach can be considered an evolution of cognitive fusion. Compared to the latter, it has the advantage of software-assisted fusion, eliminating the cognitive effort of the operator. Requiring only single perineal access, Esaote® allows the fusion biopsy to be carried out under local anesthesia on an outpatient basis, which quickens the execution time. Another advantage is that the "freehand" mode of production avoids conflict between the biopsy needle and the pelvic skeleton, especially while sampling anterior areas in very large prostates. Despite these advantages, this approach has some limitations: a) the fusion process is based on landmarks established by the operator (i.e., greater transverse diameter, glandular apex, seminal vesicles, bladder floor) and not on the overlap between the glandular contours traced on MR images and the glandular margins displayed at the US. This leads to a lack of standardization and could make the fusion process less precise by altering the quality of targeted biopsy itself, especially in larger prostates; b) detection rate is strictly dependent on the ability of the operator to navigate freehand within the prostate until the site of the target area is reached c) the patient's discomfort is comparable

Table 1. Summary of advantages and disadvantages of each transperineal fusion biopsy technique

US/MRI fusion tecnique	US/MRI fusion modality	Advantages	Disadvantages
Cognitive US/MRI fusion-targeted biopsy	The overlapping of US and MRI scans is performed exclusively by the operator's brain.	The procedure is carried out under local anesthesia on an outpatient basis. The procedure is not more expensive than a common prostate biopsy. The "freehand" mode of production avoids conflict between the biopsy needle and the pelvic skeleton, especially while sampling anterior areas in very large prostates. Prostate cancer detection rate is overlapped to those of software-assisted US/MRI fusion methods.	The lack of a standardization. The patient's discomfort due to transperineal access. The procedure depends on the skill of the surgeon in translating the SL identified at MRI examination to the images visualized at the US real-time evaluation. Detection rate strictly depends on the ability of the operator to navigate freehand within the prostate tissue until the needle reaches the target area.
Transperineal freehand US/MRI fusion target biopsy	US/MRI images fusion is assisted by a dedicated software.	Eliminating the cognitive effort of the operator. The procedure is carried out under local anesthesia on an outpatient basis. The "freehand" mode of production avoids conflict between the biopsy needle and the pelvic skeleton, especially while sampling anterior areas in very large prostates.	The fusion process is based on landmarks established by the operator. Detection rate is strictly dependent on the ability of the operator to navigate freehand within the prostate until the site of the target area is reached The patient's discomfort due to transperineal access. The patient's movements force the operator to readjust the US/MR image fusion several times during the procedure. The system does not memorize the sampling trace, which makes it impossible to repeat the same sampling during active surveillance.
Transperineal template assisted US/MRI fusion biopsy	US/MRI images fusion is assisted by a dedicated software	Reproducibility of the sample (a very important feature for all patients with are candidate to active surveillance) Spinal or general anesthesia eliminates the patient's discomfort and movements, making the fusion process optimal. The stepper integrated with the operating bed eliminates potential errors related to the movement of the operator's arm.	This procedure requires the access to the surgery room. The procedure is more expansive. The procedure required multiple. access to the perineum. The path of the needle through the perineum is obliged by the template. This makes difficult to take samples from the anterior portion of the gland due to possible conflicts between biopsy needle and pelvic skeleton in patients with a small pelvis and large prostate.

US/MRI: ultrasound/magnetic resonance imaging

to that of an ambulatory biopsy with TP access; d) the patient's movements (accentuated by the discomfort) force the operator to readjust the US/MR image fusion several times during the exam; d) the system does not memorize the sampling trace, which makes it impossible to repeat the same sampling during active surveillance.

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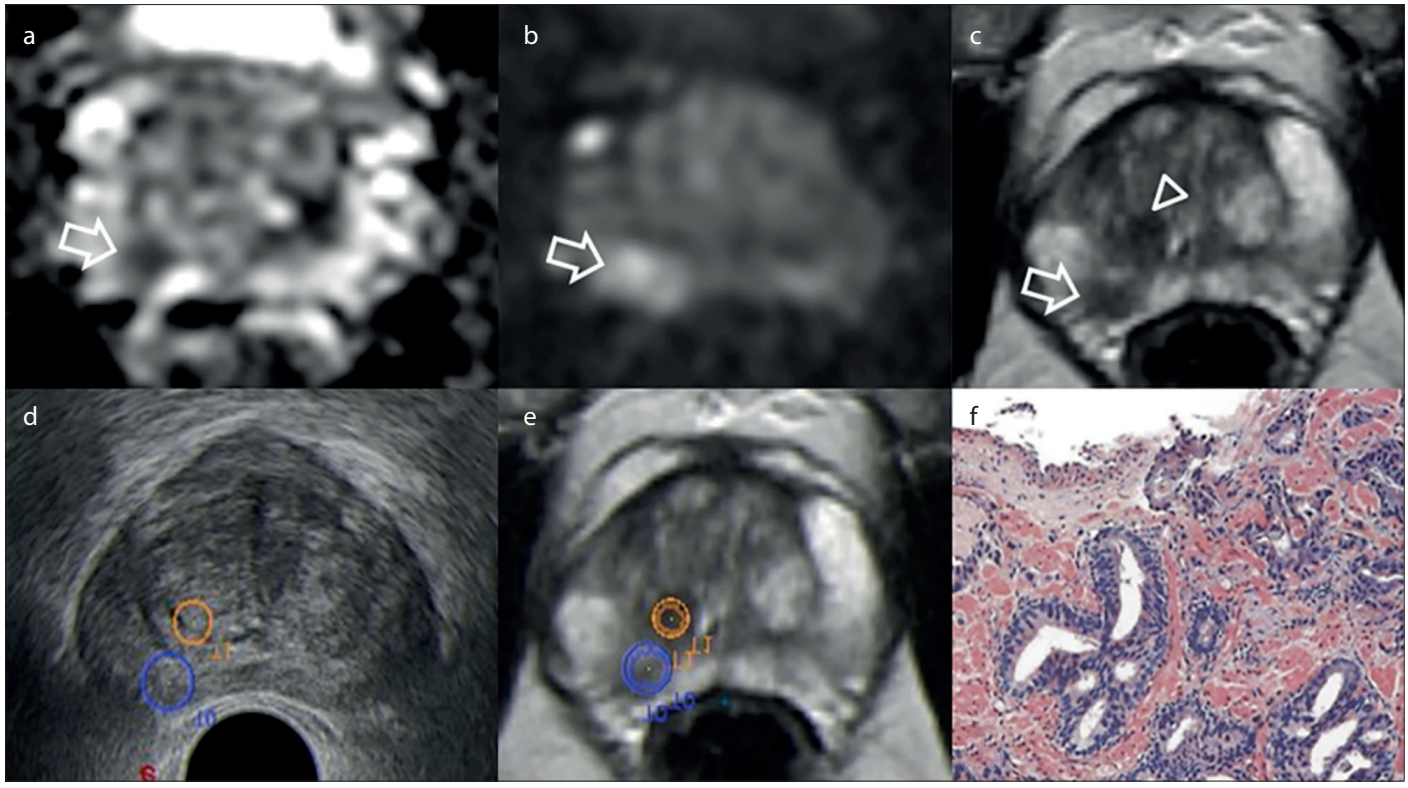

Figure 1. a-f. Biparametric MRI of the prostate at 1.5 T without endorectal coil in a 58 year-old patient with elevated PSA (7.3 ng/mL). Biparametric MRI shows in the mid of the gland in the right peripheral zone a hynomogeneous marked hypointense area on ADC (arrow in a), hyperintense on high b-value diffusion-weighted imaging (arrow in b), and hypointense on T2-weighted sequences (arrow in c) (S-PIRADS category 4 lesion); note on T2-weighted image (arrow-head in c) an hypointense area in right posterior transition zone. Transperineal US (d) and T2-weighted image (e) before fusion process for targeted biopsy. Histology of T0 target lesion: adenocarcinoma Gleason 7 (3+4) (f); Histology of T1 target lesion: chronic prostatitis (f)

BiopSee® system (MedCom GmbH, Germany): Transperineal Template assisted US-MRI fusion biopsy

BiopSee® was developed in Germany by MedCom GmbH, a company founded in 1997 that offers specialized telemedicine products and innovative imaging solutions in oncology, interventional radiology, and surgery.

BiopSee® platform is a US system that enables the import of MRI data sets. The DICOM FILES icon allows the operator to import the T2W sequences of the prostate MRI from a CD. Once the sequences have been imported, the CONTOURING TAB is used to outline the prostate and the SL with the contouring tools consecutively until the entire volume of the gland and the SL is demarcated.

The Contours-Save to database function allows storage of the contoured MRI sequences. The patient is placed in a lithotomic position after general or spinal anesthesia. The US probe mounted on a stepper that is solidarized to the operating bed is introduced into the patient's rectum. The US scan of the gland is performed in a craniocaudal direction after pressing the "START ACQUISITION" key. At the end of the procedure, the operator presses the "STOP ACQUISITION" key. In this step, a bidimensional (2D) TRUS acquisition of the prostate is performed from the base to the apex of the gland. Then BiopSee® automatically processes these sequences providing a 3-D US reconstruction of the gland.

The "FUSION" step consists of superimposing the contours of the MRI on the US anatomy of the prostate. This is achieved by clicking on the "ENABLE FUSION" function which allows the operator to superimpose the T2W sequence on US sequence using the appropriate rotation commands.

The next step is to plan the biopsy samples. On the "Note for Configuration" window after clicking the virtual template icon, the operator can plan the location of the biopsy cores. Then, the software indicates the access point of the needle to the operator using the perineal template based on a programmed virtual template (the software transfers the coordinates from the virtual template to the perineal template). Finally, the fusion-targeted biopsy is performed and the needle, through a perineal template, passes through the prostate along a longitudinal trajectory (parallel to the US probe) till the target area. All samples should be collected in blocks, named according to the sampling area, and

sent separately for histopathological examination. After each biopsy, the exact 3-D pickup location is recorded and stored by the software.

One of the advantages of the BiopSee® system is the reproducibility of the sample, a very important feature for all patients with low risk lesions under active surveillance. Moreover, for focal treatments (ex: HIFU, Cryotherapy, HDR Brachytherapy, Electrophoresis, etc.), BiopSee® allows the Dicom of the biopsy plane (contours, withdrawal points, trajectories, coordinates, etc.) to be exported to other software. Spinal or general anesthesia eliminates the patient's discomfort and movements, making the fusion process optimal and easing the postoperative recovery. The stepper integrated with the operating bed eliminates potential errors related to the movement of the operator's arm.

The main disadvantages of the system are: a) the need for multiple access routes to the perineum; b) the path of the needle through the perineum is obliged by the template. This makes it difficult to take samples from the anterior portion of the gland due to possible conflicts between biopsy needle and pelvic skeleton in patients with a small pelvis and large prostate. The advantages and disadvantages of each fusion biopsy techniques are summarised in Table 1.

In conclusion, in this narrative review, we summarized the current knowledge about prostate MRI and transperineal US/MRI fusion-targeted biopsy in the scientific literature. The PI-RADS v2 system through mpMRI is the most commonly used risk stratification system even if the bpMRI-S-PIRADS system solves problems such as gadolinium toxicity and ambiguity related to PIRADS 3 risk category.

Transperineal access offers a lot of advantages for US/MRI fusion devices. Different techniques and devices are available to perform transperineal US/MRI fusion-targeted biopsy. Each technique presents its own pros and cons over the others but all techniques report similar detection rates. No definitive data are available concerning the superiority of one technique over the others.

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