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Original article

In-bore MRI targeted biopsy

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Summary. Clinical suspicion of Prostate Cancer (PCa) is largely based on increased prostate specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) and/or positive imaging and, up today, biopsy is mandatory to confirm the diagnosis. The old model consisted of Standard Biopsy (SBx), that is random sampling of the prostate gland under ultrasound guidance (TRUS), in subjects with clinical suspicion of PCa. This involves the risk of not diagnosing a high percentage of tumors (up to 30%) and of an incorrect risk stratification. Multiparametric Magnetic Resonance Imaging (mpMRI) has transformed the diagnostic pathway of PCa, not only as an imaging method for detecting suspicious lesions, but also as an intraprocedural guidance for Target Biopsy (MRI-TBx), thus bridging the diagnostic gap. Several single and multicenter randomized trials, such as PROMIS, MRI first, PRECISION and that reported by Van der Leest et al. have confirmed the superiority of the "MRI pathway", consisting of mpMRI and MRI-TBx of suspicious lesions, over the "standard pathway" of SBx in all patients with elevated PSA and/or positive DRE. MRI-TBx appears to be advantageous in reducing the overall number of biopsies performed, as well as in reducing the diagnosis of clinically insignificant disease while maintaining or improving the diagnosis of clinically significant PCa (cs-PCa). Moreover, it shows a reduction in the diagnosis of ins-PCa, and therefore, of overdiagnosis, when using MRI-TBx without sacrificing performance in the diagnosis of cs-PCa. In light of these results, the European Association of Urology (EAU) has introduced the concept of MRI-TBx into its guidelines for the PCa diagnostic process, with a specific indication to perform prostate mpMRI before any biopsy (level of evidence IA); in the clinical practice of our Institute, in-bore MRI-TBx is the preferred technique, as it allows even very small lesions to be sampled, detects more cs-PCa and less ins-PCa than SBx, and have a lower percentage of upgrades after surgery. (www.actabiomedica.it).

Keywords: prostate cancer, multiparametric Magnetic Resonance Imaging (mpMRI), MRI-Targeted Biopsy, in-bore biopsy

Background

Clinical suspicion of Prostate Cancer (PCa) is largely based on increased prostate specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) and/or positive imaging and, up today, biopsy is mandatory to confirm the diagnosis.

The old model consisted of Standard Biopsy (SBx), that is random sampling of the prostate gland under ultrasound guidance (TRUS), in subjects with clinical suspicion of PCa. This involves the risk of not diagnosing a high percentage of tumors (up to 30%) and of an incorrect risk stratification (1).

Multiparametric Magnetic Resonance Imaging (mpMRI) has transformed the diagnostic pathway of PCa, not only as an imaging method for detecting suspicious lesions, but also as an intraprocedural guidance for Target Biopsy (MRI-TBx), thus bridging the diagnostic gap.

Several single and multicenter randomized trials, such as PROMIS (2), MRI first (3), PRECISION (4) and that reported by Van der Leest et al. (5) have confirmed the superiority of the "MRI pathway", consisting of mpMRI and MRI-TBx of suspicious lesions, over the "standard pathway" of SBx in all patients with elevated PSA and/or positive DRE. MRI-TBx appears to be advantageous in reducing the overall number of biopsies performed, as well as in reducing the diagnosis of clinically insignificant disease while maintaining or improving the diagnosis of clinically significant PCa (cs-PCa).

In particular, comparison between the MRI-TBx and SBx pathways, followed in the PRECISION study by 252 and 248 patients, respectively, has demonstrated cs-PCa in 38% of patients with MRI-TBx vs. 26% with SBx. The percentage of patients with findings of insignificant PCa (ins-PCa) was 9% with MRI-TBx vs. 22% with SBX. Moreover, this improved performance was accompanied by a 28% reduction of biopsies (MRI-TBx vs SBx), because men with negative mpMRI did not receive prostate biopsy (4).

Similar results have been obtained in the MRI FIRST study (3) and the study by Van der Leest et al. (5)setting, and population: A prospective, multicenter, powered, comparative effectiveness study included 626 biopsy-naïve patients (from February 2015 to February 2018, both of which showed a reduction in the diagnosis of ins-PCa, and therefore, of overdiagnosis, when using MRI-TBx without sacrificing performance in the diagnosis of cs-PCa.

In light of these results, the European Association of Urology (EAU) has introduced the concept of MRI-TBx into its guidelines for the PCa diagnostic process, with a specific indication to perform prostate mpMRI before any biopsy (level of evidence IA) (6). Highlighting the risk of missing cs-PCa (4.9%) (5), they recommend that suspicious lesions at mpMRI in biopsy naïve patients undergo MRI-TBx along with SBx. The most practical technique to perform such a combination of biopsies is with mpMRI-US fusion, as it allows both targeted and systematic sampling within the same sitting.

For patients with a previous negative SBx and positive mpMRI, on the other hand, only MRI-TBx need be performed (7). In this case, in-bore MRI-TBx is the preferred technique in the clinical practice of our Institute, as it allows even very small lesions to be sampled, detects more cs-PCa and less ins-PCa than SBx, and have a lower percentage of upgrades after surgery (8).

In-bore Technique

A manual system for in-bore MRI-TBx (DynaTRIM® Targeted Trans-Rectal Interventional MRI, Invivo, Gainsville, FL, US) first entered use in our Institution in 2014. As illustrated in Fig. 1, during the use of this system the patient assumes a prone position on MRI bed, the introducer is put into the rectum and then connected to the device. The movement of the introducer is determined by an imaging registration software that forms part of the system. After MRI image acquisition, the software indicates how many degrees to rotate the introducer around each of two axes, and how far to advance longitudinally in order to guide the needle into the target lesion. Positioning of the introducer in this way however, is not always precise due to the limits of the system (related for example

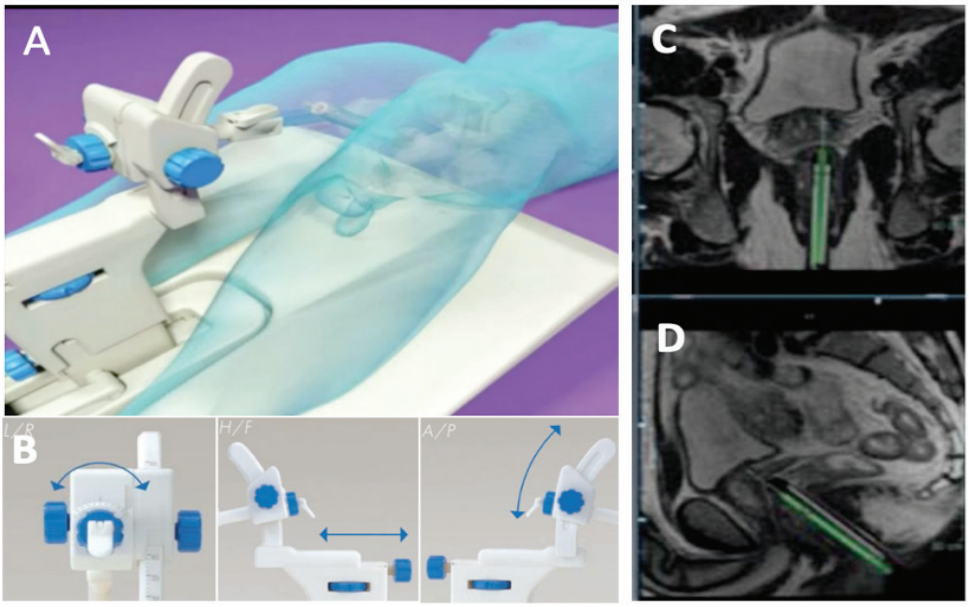


Fig. 1 "Manual System for In-Bore MRI-TBx" – Insertion of introducer in rectum of patient in prone position (**A**); Device movement determined by applying two rotations and longitudinal translation (**B**); Axial (**C**) and para-sagittal (**D**) T2 weighted (T2W) images are obtained for initial guidance. These images were sent to a dedicated planning workstation where the radiologist identifies the current needle guide position and the target lesion. The software then calculates the adjustments needed to reposition the needle guide such that the needle trajectory arrives at the target lesion.

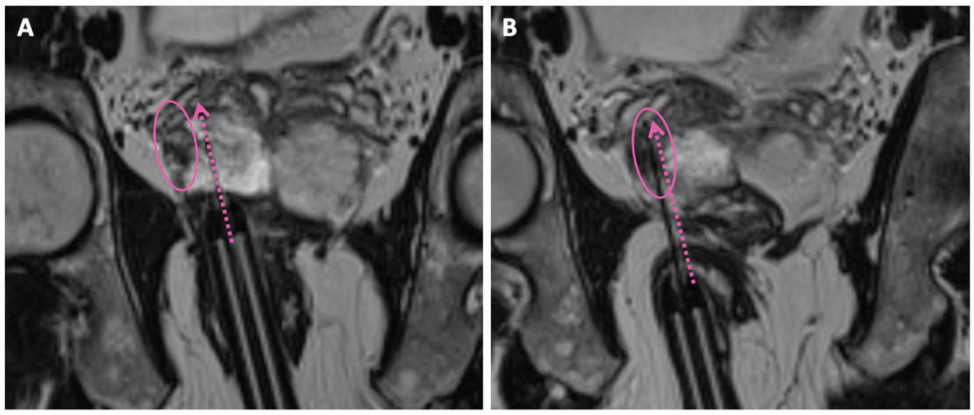


Fig. 2 "Manual adjustment of needle trajectory" - Manual in-bore MRI-TBx performed in Patient with the target lesion located on the base of the right Peripheral Zone (PZ) of the gland. Note the needle guide pointing at the suspicious lesion and, from left (**A**) to right (**B**), with fine manual adjustments, it has been possible to sample the most suspicion area of the lesion.

to resistance to movement by the rectum, and operator variability in applying the indicated rotations and translation), but the operator can manually adjust the trajectory to better orient the introducer and needle towards the target identified on the MRI (Fig. 2). In our experience, we have found that relative to applying the rotations indicated by the software further manual adjustment increases the percentage of samples with PCa diagnosis by 92.3% (9).

In 2018, a second, robotic device for in bore MRI-TBx (Soteria RCM® Remote controlled manipulator, Soteria Medical, Arnhem, The Netherlands) was

introduced into our practice. It has a pneumatic robotic arm, that provides more freedom of movement for manipulating the introducer, and an imaging registration software able to directly move the introducer. It also provides a projection of the needle trajectory, based on post-movement images to verify the correct orientation towards the target, allowing greater confidence in the procedure and thus saving time (Fig 3, 4).

Key Indications

Patients with previous negative biopsy and positive mpmri (Clinical Case 1)

According to EAU Guidelines (Level of evidence IIA) (6), patients with previous negative biopsy and positive mpMRI should undergo only a MRI-TBx. This is because it has been demonstrated that adding

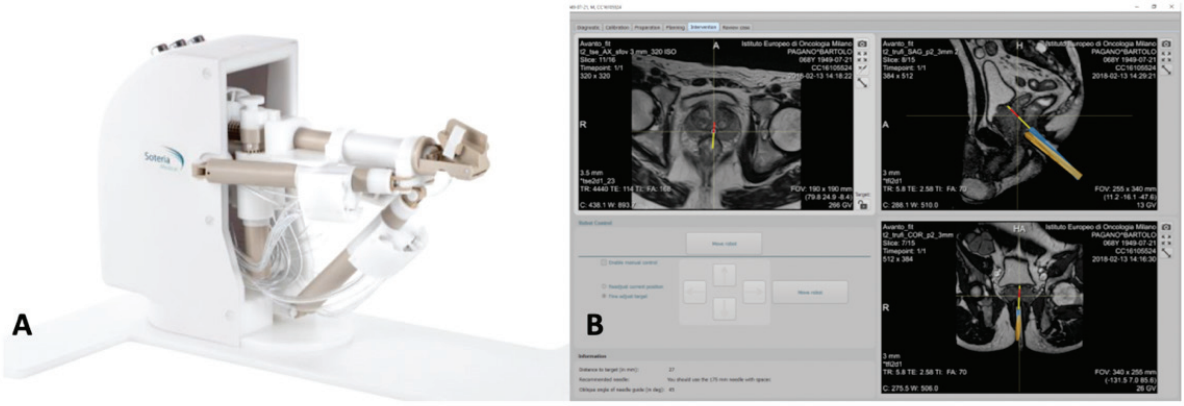


Fig. 3 "In-bore Robotic System" – **A.** Robotic arm; **B.** The same initial planning images are obtained and sent to the dedicated workstation where the radiologist indicates the needle guide and target lesion locations. On command from the radiologist, the robot then repositioned the needle guide to point in the direction of the lesion.

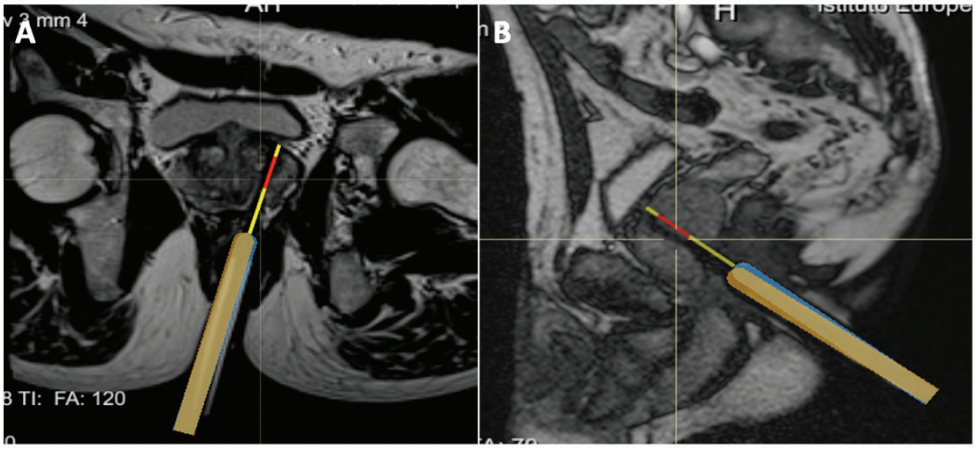
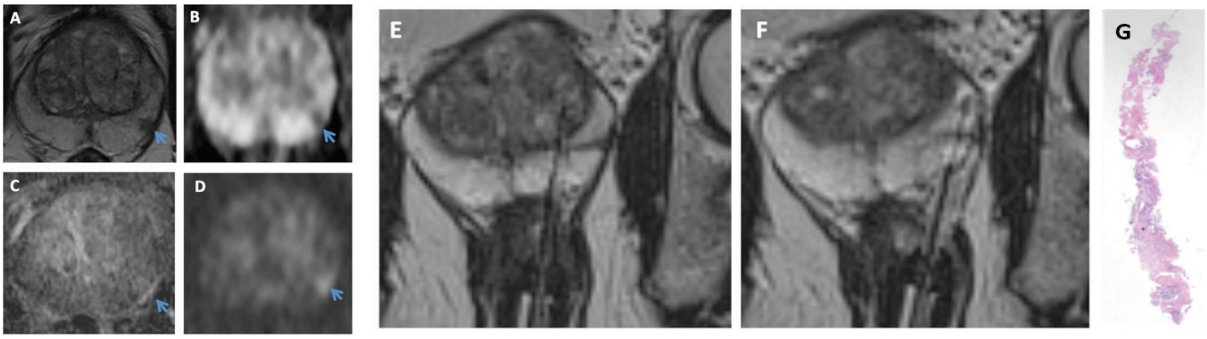


Fig. 4 "Robotic adjustment of needle trajectory" – The software automatically simulated the predicted needle position and overlaid this on the images, providing an estimate of position of the sampling part of the needle relative to the lesion without having to insert the needle. After the movement of the robot, further images are acquired to check if the projection of the sampling part of the needle is correctly positioned within the lesion (totally or at least in part) (**A, B**). If the predicted needle position did not correspond to the lesion, the radiologist could repeat the above procedure of target definition and repositioning of the needle guide until an acceptable correspondence was reached

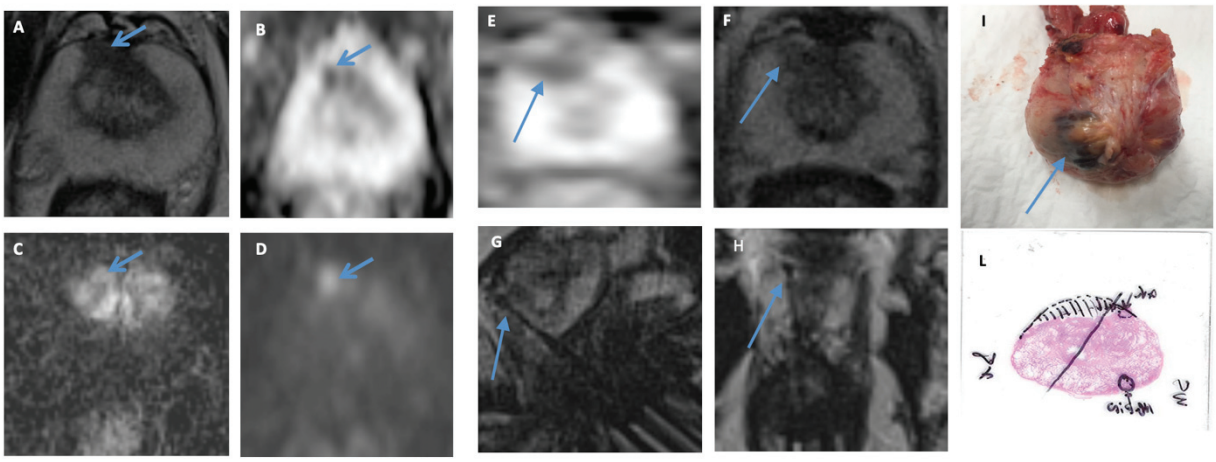


Clinical Case 1. 70-year-old man, with PSA 9.2 ng/mL, negative DRE and Atypical Small Acinar Proliferation (ASAP) finding at TRUS-SBx in 1/14 cores. At pre-biopsy mpMRI a 4 mm lesion, with a Prostate Imaging Recording and Data System (PI RADS) score of 4, was found in the left PZ, characterized by circumscribed hypointensity <15mm on T2W sequence (**A**), focal markedly <15mm hypointensity on Appearent Diffusion Coefficent (ADC) map/ hyperintensity on Diffusion Weight Images (DWI) high b-value image (**B, D**) and no focal early enhancement (**C**). An in-bore MRI-TBx was performed: the first core was acquired near the lesion, with pathological next result of normal parenchyma (**E**); after manual adjustment, the second core was acquired directly into the target, with the following pathological result of 70% of Adenocarcinoma, Gleason Score (GS) 3+4 (**F, G**).

SBx, the cs-PCa detection rate increases only of 2.7%, such that detecting a single cs-PCa at least 37 additional SBx have to be performed (10).

Biopsy naïve patients, only in selected cases (Clinical Case2).

In biopsy naïve patients, EAU Guidelines recommend both SBx and MRI-TBx on the suspicious lesions. However, in selected groups of patients, those with PI RADS 3, 4 and 5 lesions and/or lesions of less than 10 mm and/or lesions located in anatomical sites difficult to reach with biopsy (anterior apex or cranial zone), in-bore MRI-TBx may play a role. Of course, the patients should be carefully selected because the risk of missing cs-PCA when using just MRI-TBx in biopsy naïve patients rises to 4.9%; in other words, every 20 SBx procedures an additional cs-PCa is diagnosed (9).



Clinical Case 2. 65 years old man, with PSA 3.2 ng/mL steadily increasing, negative DRE and no previous biopsy; at pre-biopsy mpMRI a 5mm PI RADS 4 lesion was found in the right anterior PZ, with circumscribed hypointensity <15mm on T2 (**A**), focal markedly <15mm hypointensity on ADC map/hyperintensity on DWI (**B, D**) and focal early enhancement (**C**). During pre-biopsy MRI, the lesion was firstly identified on ADC map and axial T2W plan (**E, F**), then reached by the needle (**G, H**), with a final diagnosis of GS 4+3. Final histology after prostatectomy disclosed a pT3aN0 stage and confirmed the GS 4+3 (**I, L**).

In a meta-analysis of 29 studies (including 13,845 patients) however, Goldberg et al. argued that by avoiding SBx, the percentage of ins-PCa is reduced without affecting the ability to diagnose cs-PCa, underlining the potential of MRI-TBx alone (11).

Reclassification (Clinical Case 3)

In patients with mpMRI features suggesting the presence of a primary GS 4 (for example: reduced ADC values, large volume lesion, undiagnosed extraprostatic extension), but SBx only shows a GS 3+3 (12), in bore MRI-TBx should be performed for possible reclassification, in order to personalize treatments (13,14).

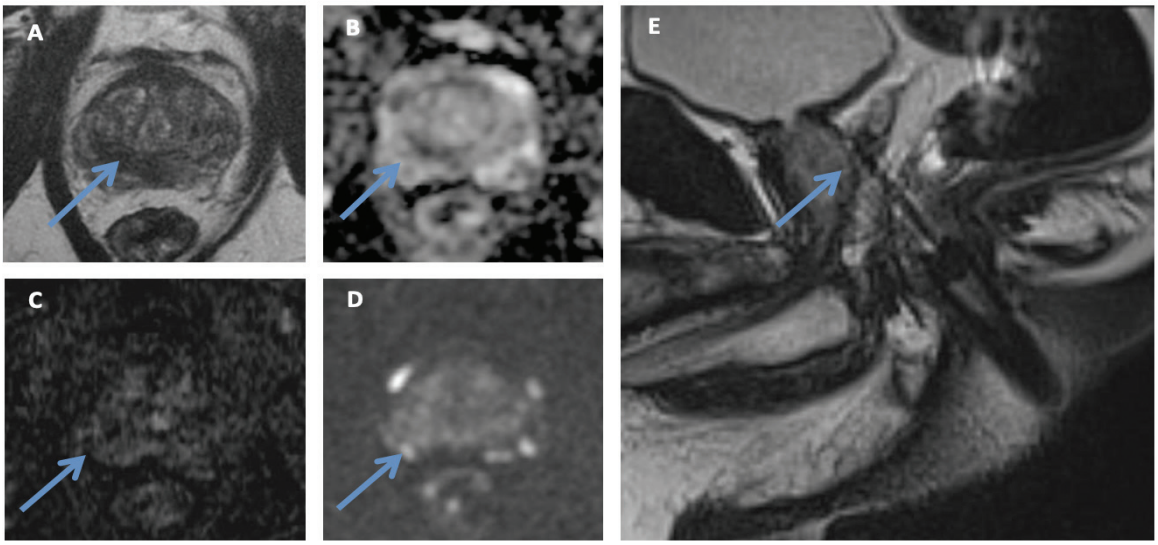
Controversial Areas

Number of cores

There is currently no agreement in the literature or in the urological and radiological communities on the number of cores needed to correctly diagnose PCa, on the best target sampling path or on the best spatial distribution of intra-target cores.

In their latest document, the PI-RADS Steering Committee (15) suggest trying to resolve these issues by introducing the concept of "focal saturation" to indicate the sampling of the target lesion and its "penumbra" in biopsy naïve patients or in patients with previous negative SBx. While not precisely described in the text, the term "penumbra" is presumably meant to refer to the area around the target.

To test the suggested approach, we retrospectively evaluated all 219 of the 414 in-bore MRI-TBxs performed with manual device, all 81 of 283 in-bore MRI-TBx performed with robotic system that satisfied criteria for focal saturation in the ata archive of our institution. With the manual system, 100% of the diagnostic rate was obtained with the first four samples and no additional PCa diagnosis was obtained beyond the fifth core, while with the robotic system, 100% of the diagnostic rate was obtained with the first three samples, that is no additional PCa diagnosis was obtained beyond the fourth core. Therefore, from our



Clinical Case 3. 70 years old man, with PSA 7.98 ng/mL, negative DRE and diagnosis of GS 3+3 in 3/14 at SBx, suitable to Active Surveillance (AS, <20% +ve cores, <50% core involvement, GS 3+3, PSA <10ng/mL, cT1c) [6]; at pre-biopsy mpMRI a 15mm PI RADS 5 lesion was found in the right Central Zone (CZ), with circumscribed hypointensity > 15mm on T2W images(**A**), focal markedly > 15mm hypointensity on ADC map/hyperintensity on DWI (**B, D**) and focal early enhancement (**C**), with suspicious seminal vesicle infiltration. After discussion of the case at multidisciplinary team, a MRI-TBx was perfomed (**E**), resulting in a GS 4+3 and thus fitting the patient for surgery, with a final staging of pT3b N0 M0.

experience, the optimal number of samples needed for focal saturation to diagnose PCa with a 100% diagnostic rate is 4 for the manual system and 3 for robotic procedures.

Biological equivalence

Accurate risk stratification is a cornerstone of modern PCa management (16, 17), and the introduction of MRI-TBx into the diagnostic pathway has raised the question as to whether the risk of upgrading of the GS, after radical prostatectomy differs between MRI-TBx and SBx.

In a recent study, published in 2020 by Ahdoot et al. (18), 404 patients undergoing prostatectomy were analyzed to compare the histopathological results of SBx and MRI-TBx with the final histopathology obtained after surgery. They was observed that, for the same patients, the degree of GS upgrade was 41.6% with SBx, 30.9% with MRI-TBx and 14.4% if both SBx and MRI-TBx were considered. These results are in agreement with existing data in the literature, where the median percentage of GS upgrade after surgery is 20-30% when comparing in bore MRI-TBx with whole-mount histopathology (5, 19-21).

From our experience with 168 patients, the overall agreement was 30%; considering only those with GS 3+3 at in-bore MRI-TBx, however the upgrade rate was high (64.3%) from biopsy to radical prostatectomy. We concluded that for GS 3+3, this indicates the necessity to integrate biopsy GS with mpMRI results before adopting a less invasive treatment. A lower rate of upgrading was observed for patients with a diagnosis of GS 3+4 and 4+3 (19.6% and 4.8% respectively) which suggest a safely plan active treatment.

A possible risk introduced by MRI-pathway is the so-called "*Will Rogers phenomenon*", the potential displacement of patients with less aggressive high-grade PCa from a group with classically favourable outcomes to a group with less favourable ones. In this way, the first group becomes less "contaminated" by patients with high-grade PCa, improving the overall outcome. Similarly, the second group will present a potentially more favourable high-risk disease, improving outcomes in this group as well.

This could have clinical implications, especially for men who are suitable for AS or radical treatment, so the validation of risk calculators using this data from targeted biopsies, as the technique becomes widely adopted, will be mandatory (22).

Patient acceptability

A final, controversial area relates to the acceptability by the patient of different biopsy procedures. To better understand these views, we assessed 47 patients with an ad-hoc questionnaire with 11 questions on a visual analog scale (VAS) of points from 0 (not satisfied) to 10 (very satisfied). Feedback was positive regarding MRI-TBx, particular for the perceived usefulness (9.2) and perceived possibility to ask questions (9.0), though a few patients complained about pain (21%), immobility (10%) and duration (4%). Out of 47 patients enrolled, 24 had previously had SBx. In 10 questions provided, the results were in favour of in-bore MRI-TBx; only for duration was there a preference for SBx. In addition, 75% of the respondents stated, if necessary, that they preferred in bore MRI-TBx instead of SBx.

Conclusions

MRI-TBx is a procedure practicable within a reasonable time and it is based on a specific clinical assumption. Future studies to answer emerging clinical questions are mandatory.

Human and Animal Rights and Informed: 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 Declaration of Helsinki and its later amendments or comparable ethical standards.

Authors Contribution: Each author has contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision and final approval.

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

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