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MRI/TRUS fusion software-based targeted biopsy: the new standard of care?

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ABSTRACT

The advent of multiparametric MRI has made it possible to change the way in which prostate biopsy is done allowing to direct biopsies to suspicious lesions rather than randomly. The subject of this review relates to a computer-assisted strategy, the MRI/US fusion software-based targeted biopsy, and to its performance against the other sampling methods. Different devices with different methods to register MR images to live TRUS are currently in use to allow software-based targeted biopsy. Main clinical indications of MRI/US fusion software-based targeted biopsy are re-biopsy in men with persistent suspicious of prostate cancer after first negative standard biopsy and the follow up of patients under active surveillance. Some studies have compared MRI/US fusion software-based targeted versus standard biopsy. In men at risk with MRI-suspicious lesion, targeted biopsy consistently detects more men with clinically significant disease as compared to standard biopsy; some studies have also shown decreased detection of insignificant disease. Only two studies directly compared MRI/US fusion software-based targeted biopsy with MRI/US fusion visual targeted biopsy, and the diagnostic ability seems to be in favor of the software approach. To date, no study comparing software-based targeted biopsy against in-bore MRI biopsy is available. The new software-based targeted approach seems to have the characteristics to be added in the standard pathway for achieving accurate risk stratification. Once reproducibility and cost-effectiveness will be verified, the actual issue will be to determine whether MRI/TRUS fusion software-based targeted biopsy represents anadd-on test or a replacement to standard TRUS biopsy.

INTRODUCTION

The diagnosis of PCa has been based on transrectal US (TRUS) - currently standardized as a 12-core sampling strategy. This test has undergone considerable modification in order to improve the efficiency of the sampling. The original 6 cores proved to miss too much cancer [1]; inflating the number of cores beyond 12 conferred marginal incremental benefit in terms of detection[2][3]. Despite the standardization of the test, there is wide consensus that 12-core TRUS biopsy remains prone to errors. These principally comprise over-diagnosis of insignificant disease as well as missed diagnosis and mis-classification of clinically significant disease [4-6].

The advent of multiparametric magnetic resonance imaging (mp-MRI) has made it possible to change the way in which prostate biopsy is done - other than by increasing the number of needle deployments dedicated to the prostate. The information on tumour location and extent that is conferred by mp-MRI has allowed us to over-sample the target volume and under sample or not sample the non-target volume [7]. There are three ways in which this can be done: in-bore MRI biopsies; MRI/US fusion visual targeted biopsies; and MRI/US fusion software-based targeted biopsies. These three approaches are all informed by tumour location and are, as a result, similar. Moreover, the target volume is generated by a shared source – the MRI. It is just the manner in which the target volume is 'represented' to the operator that separates them. This being the case, it can be argued that the most direct method is the in-bore approach as the signal that generates the target is used to guide and verify that the needles are within the target. The other two methods use an alternative interface (the brain or a computer-derived model of the prostate) to carry the information derived from the MRI onto the platform (ultrasound) that will be used to conduct the biopsy. The subject of this review relates to the use of a computer model to assist in targeting an MRI-derived target, and to its performance against the other sampling methods.

INTERPRETATION AND REPORTING OF MULTIPARAMETRIC MRI

The MRI acquisition and reporting by the radiologist is the initial step of all MR targeted biopsy strategies. mp-MRI includes three components: high-resolution T2-weighted MR images (T2WI) and at least two functional MRI techniques including diffusion weighted imaging (DWI) and either dynamic contrast enhanced MRI (DCE-MRI) or MR spectroscopic imaging (MRSI) (Figure 1).

T2WI reflects water content of tissues. This technique has high spatial resolution that can better define the prostate zonal anatomy and the presence of PCa as focal area of low signal intensity, frequently with nodular or oval shape. However, T2WI alone may result in false-positive findings. Further, the PCa diagnosis in the central zone by the use of T2WI sequences poses a great challenge, given the anatomical heterogeneity and the numerous findings attributable to benign prostate hyperplasia [7].

DWI measures the random movement of water molecules. This parameter can indirectly estimate information related to the composition and the cellular density of prostatic tissue. In particular, PCa lesions have a low diffusion due to the high cellularity. By using an apparent diffusion coefficient (ADC) map, which enables the quantification of diffusion properties, the suspected lesions, appear as a hypointense area on the map. It is a widely available technique which demonstrated a better detection rate in comparison with T2WI and a strong association with tumor aggressiveness [8].

DCE-MRI permits the assessment of contrast kinetics in focal lesions. PCa typically enhances to a greater extent and faster than the surrounding normal glands, and the subsequent contrast washout is rapid. Many authors demonstrated that DCE-MRI has a value in the localization of PCa foci. In contrast, this parameter alone can also result in false-positive findings [9].

MRSI detects relative levels of choline and citrate within cancer tissue. Decreased levels of citrate and a true increase in choline peak are typically seen in PCa lesions. This parameter could improve the specificity of MRI but it significantly lacks sensitivity. Moreover, the inter-observer agreement is very low, and the post-processing is complex, leading to consider this parameter as an optional technique in most centers [10].

The use of an endorectal coil to increase the spatial resolution of the technique is still under debate, especially with the recent improve in signal-to-noise ratios achieved by the use of the 3-T scanner [11].

To describe suspected lesions diagnosed by MRI in a standardized manner, radiologists use standardized suspicion scores and graphical templates to show locations. The most used score are the 1 to 5-point Likert scale (based on radiologist's subjective score) or the PI-RADS score (based on determined criteria) [12] [13].

In particular, concerning PI-RADS score, the inter-reader agreement performs well and the inter-reader reproducibility improves with increasing experience.

MRI-GUIDED TARGETED BIOPSY STRATEGIES

A MRI targeted biopsy can be performed in three ways: in-bore MRI targeted biopsy; MRI/US fusion visual targeted biopsy; and MRI/US fusion software-based targeted biopsy.

Concerning in-bore MRI targeted biopsies, needles are introduced only into the areas of interest by performing a transrectal or transperineal biopsy. Serial MRI scans are performed to confirm biopsy needle placement. Multiple studies demonstrated that in-bore MRI targeted biopsies are feasible with a median detection rate significantly higher than random biopsies. Moreover, this approach reduces the number of sampled cores with a real-time feedback of its placement, allowing a high likelihood of hit target [14] [15]. Nevertheless, in-bore MRI targeted biopsy is time-consuming and costly, not commonly available and is performed in prone position under general anesthesia.

The simplest targeted strategy concerns the use of MRI/US fusion visual targeted biopsies directed to the suspicious areas highlighted on the MRI. The first step, as in the other strategies, is represented by the detection of suspicious lesions on MRI. Then the urologist performs a standard US-guided biopsy, either by a transrectal or a transperineal approach, trying to direct the needles towards the areas suspicious on mp-MRI. Many authors suggest better efficiency and accuracy compared to standard biopsy [16][17]. The most important disadvantage relates to the learning curve and reproducibility of this strategy. This approach requires an experienced urologist to translate the information of the mp-MRI onto real time US, which can be challenging according to the deformation and the anatomical characteristics of the prostate.

Finally, MRI/US fusion software-based targeted biopsies represent a novel approach developed to improve the accuracy of prostate biopsy, allow dissemination of the technique and permit the storage of images for future re-sampling. MRI/US fusion software-based targeted biopsy devices allow to align the pre-biopsy MR images with intra-operative TRUS in order to enable the urologist to perform targeted biopsy directed towards MR visible lesions. This approach combines the high diagnostic accuracy of MRI for detecting PCa with TRUS, which represents a procedure well mastered by urologists. The process of co-registration of MRI and US images is automatized by the use of a fusion device, and therefore the results are likely to be more consistent across different centres.

- COREGISTRATION OF MRI AND US IMAGES

MRI to US cognitive fusion is complicated by the significant deformation of the prostate shape that occurs between TRUS and MRI (with or without an endorectal coil). The software-based registration method corrects this effect to achieve better diagnostic accuracy [18].

There are basically two different methods to register MR images to live TRUS: rigid and non-rigid (elastic) registration. Both of them aim to align the MR and US images through the identification of landmarks present on both corresponding images. The outer shape of the prostate is used to match the MRI contour to the live-US image.
Elastic registration allows deformation, warping and dimensional changes between images, based on mathematical algorithms. As every prostate is different in density and elasticity these calculation are estimations. Rigid registration permits only rotational and translational variations between images, without changing the images themselves. The urologist needs to make some adjustments in case of error due to the rigid registration, using manual correction of the alignment and targeting, or using different degrees of pressure/insertion depth of the US probe.
While overlapped images obtained from rigid registration usually have discontinuous borders looking less pleasant to the eye than elastic registration, it is difficult to define which method is able to achieve better accuracy. On the one hand, elastic registration should guarantee better matching; on the other hand, some experts think the cognitive adjustment might overcome the issues encountered with rigid registration and allow better spatial precision, especially in patients having unusual gland dimensions.

- FUSION DEVICES

MRI/US fusion software-based targeted biopsy first of all requires a diagnostic mp-MRI with a report scheduling all the suspicious lesions edited by an expert uro-radiologist. mp-MRI images are loaded in the specific software and regions of interest are then outlined. The patient is positioned and a TRUS is performed, with MR images superimposed on real-time US images. Targeted biopsies directed to mp-MRI-suspicious lesions are then performed.
The different devices currently in use to allow MRI/US fusion software-based targeted biopsy are reported in Table 1.
UroNav (In Vivo Corp., Gainesville, FL, USA); Virtual Navigator (Esaote, Genoa, Italy); *Real-Time Virtual Sonography (HI RVS; Hitachi, Tokyo, Japan)*. The mechanism to track the US probe and to record biopsy needle localization is electro-magnetic, and the image registration is carried out via a rigid method, or elastic registration for minor deformations with UroNav device. Biopsies are performed using a freehand TRUS probe with a transrectal approach (a transperineal approach is also possible for the UroNav device). The UroNav system was the first office-based platform produced to allow MRI/US fusion software-based targeted biopsy, with patient recruitment beginning in 2004. The other two systems were developed as unspecific fusion platforms customized for prostate biopsy.

Artemis (Eigen, Grass Valley, CA, USA). The recording of biopsy needle localization is based on encoders located on an articulated mechanical arm, which is used to acquire US images and to perform the biopsy with a transrectal or a transperineal approach. The fusion process is done via elastic registration. The system requires contouring of landmarks on both images, MRI and US.

Urostation (Koelis, Grenoble, France). In contrast to the other platforms, the US image acquisition is automatic and the tracking system employ a 3D-TRUS probe. This advanced mechanism lead to a 3-5 seconds delay in the confirmation of each biopsy needle placement. The system of co-registration is elastic and the biopsy is performed with a freehand transrectal approach.

BioJet (D&K Technologies GmbH, Barum, Germany), *BiopSee (Pi Medical, Athens, Greece)*. In contrast to other fusion platforms, these systems use a TRUS probe with two degrees of freedom (in depth and rotation) attached to a mechanical stepper fixed to the operating table. Prostate biopsy could be performed both via a transperineal or transrectal route. The tracking system uses digital encoders located on the stepper. Both systems originally used rigid registration, but both recently developed an elastic fusion system for minor deformations.

To date, there are no available studies directly comparing the different platforms in terms of accuracy, nor detection rate.

INDICATIONS OF MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY

Current main clinical indications of MRI/US fusion software-based targeted biopsy are:

(1) Re-biopsy in men with persistent suspicious of disease after first negative standard biopsy: persistently increased PSA and/or positive DRE [19 - 24] and/or diagnosis of atypical small acinar proliferation of the prostate (ASAP) [25] or extensive (multiple biopsy sites) high-grade prostatic intraepithelial neoplasia (HG-PIN). As expected, a number of studies have shown that in this sub-group of men targeted biopsy allowed the detection of more clinically significant cancers than standard biopsy [26]. For instance, in one paired cohort study reported by Sonn et al. including 105 men with previous negative standard biopsy, a novel TRUS biopsy detected 14.7% men with significant PCa, whereas MR/TRUS fusion software-based targeted biopsy detected 21.7% [19].

(2) Follow up of patients under active surveillance (AS). Many authors evaluated fusion systems to perform confirmatory targeted biopsy in patients preferring AS. Hu et al. recently proved in a series of 113 patients that confirmatory MRI/US fusion software-based targeted biopsy resulted in reclassification in 36% of men, ranging from 24% to 100% according to the MRI score, from low to high grade respectively [27]. Sonn et al. demonstrated that in a series of 171 patients, MRI/US fusion software-based targeted biopsy was 3 times

more likely to identify cancer than standard biopsy (21% versus 7% respectively), and of the men with clinically significant PCa initially enrolled for AS 38% had disease detected only on targeted biopsies [28]. Moreover, MRI/US fusion software-based targeted biopsy permit to track the location of all biopsy cores, allowing the urologist to perform a re-biopsy in the same suspicious areas, which is mandatory in the correct follow up of patients under AS.

Some experts think there might also utility in the follow up of men suspicious for local recurrence after radical prostatectomy, external beam radiation therapy or high-intensity focused ultrasound (HIFU) [29]. Further research is needed to confirm this.

Many authors suggest also a role for MRI in guiding the first prostate biopsy [30][31]. In case of better performance of this novel diagnostic pathway in contrast with the standard, MRI/US fusion software-based targeted biopsy will play a key role in the characterization of suspicious lesions even at the first biopsy.

Finally, a recent consensus meeting has raised the question whether MRI/US fusion software-based targeted biopsies can be used to guide focal therapy [32].

MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY: RESULTS

In 2013, an international working group published the Standards of Reporting for MRI-targeted Biopsy Studies (START) recommendations to report the diagnostic studies concerning targeted biopsy versus other biopsy approaches in a standardized manner. Briefly, the recommendations were to report, for each approach separately, detection rates of clinically significant and insignificant PCa, biopsy Gleason score, and maximum cancer core length. Moreover, they recommended to report the number of previous biopsies, and, concerning MRI, description of the utilized parameter and reporting protocol, image registration technique, and radiologist experience. Finally, they concluded that a new definition of clinically significant PCa diagnosed by targeted biopsy is still needed as using classifications developed for random biopsy would lead to artificial inflation of risk [33].

- MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY VS STANDARD BIOPSY

Some studies with the aim to compare the results of MRI/US fusion software-based targeted versus standard biopsy have been published, leading to two high quality systematic reviews [26] [34]. The results of the comparison between the two approaches are shown below and in Table 2 [19, 22-24, 28, 30, 31, 35-47].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy to detect PCa?

The two approaches did not differ significantly in overall detection of PCa (Table 2). When considering a core by-core analysis, Rastinehad et al. reported an increased detection rate of MRI/US fusion software-based targeted biopsy with respect to standard biopsy (37.9% vs 12.5% respectively, $p < .001$) [44].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy to detect clinically significant PCa? and to not detect clinically insignificant PCa?

First of all, different definitions of clinically significant PCa were used in published studies; consequently, the comparison between the results is difficult. Sonn et al. compared the two different approaches using five reported definitions of PCa significance. In all cases, MRI/US fusion software-based targeted biopsy detected more clinically significant PCa and fewer insignificant PCa than random biopsy [19].

As reported in Table 2, the detection rate of clinically significant PCa is higher performing a MRI/US fusion software-based targeted biopsy than performing a standard biopsy. In the recently published study of Siddiqui et al., MRI/US fusion software-based targeted biopsy diagnosed 30% more high-risk cancers versus standard biopsy ($p < .001$) and 17% fewer low-risk cancers ($p = .002$) [47]. The same results were demonstrated by Delongchamps et al., analyzing 125 patients with PCa diagnosed on MRI/US fusion software-based targeted biopsy and/or systematic biopsy and treated with radical prostatectomy. The MRI/US fusion software-based targeted biopsy alone approach would have left only 4% of significant cancers undetected [48].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy in length of biopsy positive cores?

Puech et al. reported a statistically significant longest core cancer length in MRI/US fusion software-based targeted biopsy compared to standard biopsy (mean: 7.3 mm $\pm$ 3.8 vs. 4.6 mm $\pm$ 3.1, respectively; $p = .0001$) [40]. Others reported similar results (mean: 5.5(2–9.5) mm vs. 5(2–8) mm, respectively; $p = .88$) [22].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy in terms of more accurate grading of PCa?

Siddiqui et al. published a study including 1003 men undergoing radical prostatectomy for PCa diagnosed both by MRI/US fusion software-based targeted or standard biopsy. The sensitivity of preoperative biopsy in predicting surgical specimen pathology was 77% versus 53% for MRI/US fusion software-based targeted and standard biopsy respectively, leading to an AUC for MRI/US fusion software-based targeted biopsy significantly greater that both standard ($p = .005$) and fusion + standard ($p = .04$) biopsies [47]. In another study, a concordance of 90% was registered in primary Gleason pattern between MRI/US fusion software-based targeted biopsy and radical prostatectomy specimens [50].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy detecting PCa with fewer number of cores?

In all studies reporting this data MRI/US fusion software-based targeted biopsy necessitate fewer cores to diagnose PCa compared to standard biopsies (Table 2). In the systematic revision of Valerio et al., MRI/US fusion software-based targeted biopsies detected more clinically significant cancers using fewer cores compared with standard biopsy (median: 9.2 vs. 37.1, respectively) [26].

- Did MRI/US fusion software-based targeted biopsy outperform standard biopsy to detect PCa in different subgroups of patients?

Some authors reported that the PCa detection rate after standard biopsy is less than 30% for prostates with a volume > 40 cc compared to smaller glands [49]. In the study of Walton-Diaz et al., when stratified by increasing prostate volume, the detection rate of MRI/US fusion software-based targeted biopsy decreased but was significantly greater compared to standard biopsy in each sub-group [50].

- MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY VS TEMPLATE SYSTEMATIC BIOPSY

Concerning the comparison between MRI/US fusion software-based targeted biopsy and template systematic biopsy, Radtke et al. reported a comparative analysis of 294 consecutive patients undergoing systematic transperineal biopsy and MRI/US fusion software-based targeted biopsy. The authors reported that sampling efficiency was in favor of the second method, with 46.0% of MRI/US fusion software-based targeted biopsy versus 7.5% of systematic biopsy cores detecting PCa with a Gleason score $\geq$7. However, there was still an utility to perform systematic transperineal sampling, as 12.8% Gleason score $\geq$7 were missed by the targeted approach; the opposite occurred in 20.9%. The authors concluded that the gold standard for cancer detection is a combination of systematic and targeted cores [51].

- MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY VS MRI/US FUSION VISUAL TARGETED BIOPSY

Only two studies directly compared MRI/US fusion software-based targeted biopsy with MRI/US fusion visual targeted biopsy (Table 3) [40, 41], thus indicating the need for further studies. In details, Puech et al. reported that in 79 MR imaging targets among 95 patients, positivity for cancer was 47% with cognitive and 53% with MRI/US fusion software-based targeted biopsy (p = .16) [40]. The same results were reported in a prospective study in 125 consecutive men by Wysock et al., concluding that MRI/US fusion software-based

targeted biopsy was more often histologically informative than visual targeting but did not increase cancer detection [41].

Moreover, Cool et al. reported the results of 225 simulated targeted biopsies on suspected lesions on MRI, with MRI/US fusion visual targeted biopsy sampling the 45-48% of clinically significant lesions compared with 100% obtained with MRI/US fusion software-based targeted biopsy [52]. Delongchamps et al. indirectly compared various targeted biopsy approaches in a consecutive series of patients. They reported that rigid and elastic MRI/US fusion software-based targeted biopsies performed significantly better than standard biopsies ($p = .0065$ and $.0016$, respectively), whilst MRI/US fusion visual targeted biopsy did not perform better ($p = .66$) [31]. Finally, in a preliminary study including 32 consecutive patients, Mouraviev et al. divided 32 consecutive patients into three groups based on the method used to target the suspected lesion. They concluded that MRI/US fusion software-based targeted biopsy (using two different platforms) increases diagnostic accuracy compared with MRI/US fusion visual targeted biopsy [39].

- MRI/US FUSION SOFTWARE-BASED TARGETED BIOPSY VS IN-BORE MRI BIOPSY

To date, there are no available studies comparing these strategies.

FUTURE PERSPECTIVES

The most important issue that will have to be addressed with the current use of MRI/US fusion software-based targeted biopsy concerns its role in the diagnostic pathway. The actual scenario is represented by an existing test, the standard 12 cores biopsy. The new test, the MRI/US fusion software-based targeted biopsy, could add-on or replace the existing test. In most studies conducted to determine the diagnostic value of targeted biopsy, patients underwent MRI/US fusion software-based targeted biopsies combined with standard systematic TRUS-guided prostate biopsy in the same session. The first high quality study with a very large sample size which examined the utility of MRI/US fusion software-based targeted biopsy against standard biopsy combined was recently published by Siddiqui et al. In this paper, there was little utility to include standard biopsy in the protocol as 200 men would be needed to be additionally sampled in order to diagnose one additional high-risk PCa, missed by MRI/US fusion software-based targeted biopsy. Further, the two combined approaches lead to a change in Gleason score risk stratification in 15% of cases, of which 2% increased to high risk PCa [47].

Further evidence will be acquired in the near future when the results of ongoing trials will be available. Two large UK multicenter studies will evaluate the true diagnostic accuracy of sampling only suspicious areas using a MRI/US fusion software-based targeted approach against a valid reference test, namely

transperineal template mapping biopsies: the UK Prostate Imaging Compared to Transperineal Ultrasound Guided Biopsy for Significant Prostate Cancer Risk Evaluation (PICTURE) study [53] and the PROMIS trial (54). Further, using a randomized design, the multicenter international PRostate Evaluation for Clinically Important Disease(PRECISION) study, will evaluate the detection rates of PCa by MRI/US fusion software-based targeted prostate biopsy compared to standard 12-core TRUS prostate biopsy [55]. These studies are likely to clarify the role of MR/US fusion software-based targeted biopsy in the pathway of PCa diagnosis.

The next aspect to evaluate before adopting the new procedure as a new standard of care will be cost-effectiveness. Certainly, the time spent to co-registrate MRI and US images and to perform the biopsy is longer for MRI/US fusion software-based targeted prostate biopsies compared to standard approach. Recently, Shoji et al. reported that the number of cases to perform a MRI/US fusion software-based targeted prostate biopsy within 20 minutes was 5 [46]. With regard to cost, while the fusion biopsy itself has some intrinsic expenses, the greatest increase in cost is due to the necessity to perform MRI on each patient. Nevertheless, some initial studies have shown that the overall cost-effectiveness might be still in favour of a software-based approach [56]. Economic modelling using robust data from ongoing trials will assess this key issue.

CONCLUSIONS

In men at risk with MRI-suspicious lesion, MRI/US fusion software-based targeted biopsy consistently detects more clinically significant diseases as compared to standard biopsy. Whether this novel procedure should be a replacement test or an add-on test to standard TRUS biopsy in selected groups of men will be determined by ongoing trials.

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