INTEGRATED US-MR FUSION IMAGES AND MR TARGETED BIOPSIES. WHAT ARE THEIR ROLE AND VALUE IN THE DETECTION AND FOLLOW-UP OF PROSTATE CANCER

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Summary.- Accuracy of multiparametric MRI has greatly improved the ability of localizing tumor foci of prostate cancer. This property can be used to perform a TRUS–MR image registration, new technological advance, which allows for an overlay of an MRI onto a TRUS image to target a prostate biopsy toward a suspicious area. Three types of registration have been developed: cognitive-based, sensor-based, and organ-based registration. Cognitive registration consists of aiming a suspicious area during biopsy with the knowledge of the lesion location identified on multiparametric MRI. Sensor-based registration consists of tracking in real time the TRUS probe with a magnetic device, achieving a global positioning system which overlays in real-time prostate image on both modalities. Organ based registration does not aim to track the TRUS probe, but the prostate itself to compute in a 3D acquisition the TRUS prostate shape, allowing for a registration with the corresponding 3D MRI shape. The concept of an MR-US fusion TB strategy only is gaining more and more widespread acceptance. In a TB only strategy, fewer men could be biopsied overall, with a greater proportion of men diagnosed with clinically significant prostate, as well as fewer men “over diagnosed” with clinically insignificant cancer. However, more clinical research is required before this strategy is ready for widespread adoption.

Keywords: Prostate cancer. TRUS biopsy. MRI. Fusion.

Resumen.- La precisión de la RMN multiparamétrica ha mejorado ampliamente la habilidad para localizar focos tumorales de cáncer de próstata. Esta propiedad puede utilizarse para realizar el registro de imagen de RMN en la ecografía transrectal, un nuevo avance tecnológico que permite superponer la RMN sobre la imagen de ecografía transrectal para dirigir una biopsia prostática hacia una zona sospechosa. Se han desarrollado tres tipos de registros: basados en lo cognitivo, basados en sensores y basados en el órgano. Los registros cognitivos consisten en apuntar a una zona sospechosa durante la biopsia con el conocimiento de la localización de la lesión identificada en la RMN multiparamétrica. Los registros basados en sensores consisten en el seguimiento en tiempo real del transductor de ecografía transrectal con un dispositivo magnético, consiguiendo un sistema de posicionamiento global (GPS) que se superpone a la imagen prostática en tiempo real en ambas modalidades. Los registros basados en el órgano no buscan seguir la sonda transrectal sino la propia próstata para computar en una adquisición 3D las formas en ultrasonido transrectal de la próstata, ofreciendo un registro con la correspondiente forma 3D de RMN. El concepto de la estrategia de biopsia guiada sólo por...
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INTRODUCTION

Accuracy of multiparametric MRI (MP-MRI) has greatly improved the ability of localizing tumor foci of prostate cancer. This property can be used to perform a TRUS–MR image registration or “fusion”, which allows for an overlay of an MRI onto a transurethral ultrasound (TRUS) image to target a prostate biopsy toward a suspicious area. The aim of this review is to describe the different techniques of US-MR fusion, to summarize the rational and potential value of such techniques in prostate cancer detection and follow-up, as well to draw the perspectives and current limitations of US-MR fusion targeted biopsy (TB) strategy.

1. Techniques of US-MR fusion used for prostate TB and clinical evaluation

Three types of registration have been developed: cognitive-based, sensor-based, and organ-based registration.

Cognitive registration

Consists of aiming a suspicious area during biopsy with the knowledge of the lesion location identified on MP-MRI. MRI and TRUS images are superimposed by a cognitive overlay of TRUS and MR images during biopsy, using a printed document or by displaying MR images on the screen of a workstation. The value of this technique has been supported by at least 3 retrospective analysis (1-3) comparing cognitive TB over systematic biopsies (SB). However, the accuracy of such technique is controverted, as other reports (4-5) suggested that cognitive-based TB did not perform better than systematic biopsies. Although cognitive registration may add some value to SB, it can be intuitively predicted that differences in slice orientation during acquisition between strictly axial MRI slices and the oblique scanning of end-fire TRUS probes may fail to match accurately the needle tract and the target. Moreover, the accuracy of cognitive registration also relies on the degree of expertise in prostate imaging.

Sensor-based registration

Consists of a real time tracking of the TRUS probe with a magnetic device, achieving a global positioning system which overlays prostate image on both modalities. Its main limitation is that it does not take into account prostate and patient motion during biopsy. This technique consists of a rigid geometric registration performed after paired landmarks have been selected on both TRUS and MRI (planning phase). Once TRUS–MRI overlay is deemed acceptable, the navigation system is activated (guiding phase of the biopsy), allowing for a real-time TRUS scanning and MR-guided navigation. Biopsies are performed towards the registered image, assuming that no patient movement and no displacement or deformation of the prostate by the TRUS probe occurs. However, the prostate shape on TRUS and MRI is usually different, with or without the use of an endorectal coil. Images from MRI are thus simply superimposed onto US images and prostate contour is not deformed during registration (6). Mismatches can occur during attempts to match both prostate contours and internal landmarks. Moreover, sensor-based systems only track the TRUS probe and not the prostate itself. They thus do not allow for an organ-based registration as they do not take into account the anterior displacement of the gland which occurs during TRUS scanning, leading to a loss of overlay between TRUS and MRI images (6). As a result, the topographic precision of this type of rigid registration may not exceed 5–10 mm (7). Reports having compared TB versus SB using such technique are controversial.

Organ-based registration

Mouraviev et al. (8) in a small series of 32 consecutive patients with a raising PSA level and a setting of repeat biopsy found a 46% cancer detection rate with rigid registration TB (ESAOTE navigation system, Italy), significantly higher than that of cognitive registration (33%). In another published series, Puech et al. (2) found that sensor-based registration TB (ESAOTE navigation system, Italy), although performing better than SB, did not provide a higher accuracy than that cognitive registration TB.

Palabras clave: Cáncer de próstata. Biopsia transrectal ecodirigida. RMN. Fusión.
However, it does not allow any real-time navigation because a new acquisition has to be performed after each movement of the probe. Once the target has been delineated on the MRI image registered with the reference TRUS image, a 3D-TRUS acquisition is performed with the probe aiming the assumed location of the target. A virtual biopsy is performed by aiming the presumed TRUS location of the target without activating the biopsy gun to ensure that the virtual track is through the target. An adjustment may be necessary and the virtual biopsy is repeated until matching of the needle tract and the target is obtained. Currently, only few studies are available. Portalez et al. (10), in a clinical setting of repeat biopsies, showed that the overall positive biopsy rate of TB was 36.3% versus 4.9% in SB only performed in sextants without MRI target.

Rud and co-workers (11), in a series of 90 patients referred for initial biopsy, reported a 97% biopsy success rate within the target. In our own series (5) comparing different registration techniques, the positive biopsy rate of significant cancers by organ-based registration TB was significantly higher than those of SB and cognitive TB, but not higher than that of sensor registration TB (ESAOTE, Italy).

2. Value of TB only strategy as a detection tool

Because prostate Mp-MRI is currently an established accurate technique to detect and localize significant tumor foci, the concept of an MR-US fusion TB strategy only is gaining more and more widespread acceptance (12, 13). Several issues are currently being investigated in order to confirm the value of this strategy.

a. Accuracy of Multiparametric MRI

Wide variations in acquisition protocols and the lack of robust diagnostic criteria make Mp-MRI detection of prostate cancer challenging. Also, combining different parameters is challenging. The main difficulty lies in how to take into account the different data provided by each of the MR sequences. In particular, if results between sequences are discordant, which results should be given more credit? Should data provided by each technique be balanced according to the assumed accuracy of each technique taken separately? To improve the reproducibility of Mp-MRI, the European Society of Urogenital Radiology (ESUR) recently published a unified scoring system (MR PI-RADS: Magnetic Resonance Prostate Imaging Reporting and Data System) for the detection of clinically significant tumor foci on Mp-MRI (14).

This score is based on a 5-point Likert-like scale as follow:

- Score 1: clinically significant disease highly unlikely to be present;
- Score 2: clinically significant cancer unlikely to be present;
- Score 3: the presence of clinically significant cancer is equivocal;
- Score 4: clinically significant cancer likely to be present;
- Score 5: clinically significant cancer highly likely to be present.

Despite its inherent subjectivity, this score was shown to provide clinically relevant stratification of the risk of showing PCa in a given location inside the gland (10). Crucially, a standardized report is required to define what is benign or probably benign (score 1–2), equivocal (score 3), and probably malignant or malignant (scores 4–5). In an MR-US fusion TB strategy only, follow-up of PSA level would be performed in patients with scores 1–2, and would be thus a very effective tool to avoid over-diagnosis of prostate cancer. Repeat or initial TB would be performed for scores 4–5. In the equivocal group (score 3), PSA surveillance combined with repeat MRI to update scoring or standard biopsies could be recommended. Before recommending such strategy in clinical practice, further evaluation of Mp-MRI negative predictive value is warranted to confirm the safety of PSA follow up in case of PI-RADS score 1-2. Also, further evaluation of Mp-MRI positive predictive value is needed to confirm the uselessness of performing systematic biopsies in areas with no MRI abnormality.

• Mp-MRI positive predictive value

A recent systematic review of published reports suggested that two thirds of TB were positive for cancer in biopsy-naïve patients with suspicious findings on Mp-MRI (15). Some reports also addressed the results in terms of clinically significant disease, with however the absence of radical prostatectomy specimen as reference standard, which probably induced important bias. In the study from Haffner et al (1), clinical significance was defined as any cancer core length>5 mm or any Gleason pattern>3. In this study the targeted approach was performed cognitively and detected cancer in 236 of 555 men (43%) with the standard approach detecting cancer in 248 of 555 men (45%). Of 302 cancers detected,
249 (82%) were significant prostate cancers and 53 (18%) were non-significant prostate cancers. Extended systematic biopsies did not detect 12 significant prostate cancers and targeted biopsies did not detect 13 significant prostate cancers. For significant prostate cancer detection, sensitivity, specificity and accuracy of targeted biopsies were 0.95, 1.0 and 0.98.

The true positive predictive value of Mp-MRI is however difficult to estimate, because it is biased by the result of TB, which is itself depending on the precision of targeting, the number of cores performed as well as the location of the target (some areas being more difficult to biopsy). A targeted biopsy that misses a true focus of prostate cancer that was correctly detected and localized on Mp-MRI will appear as an MRI false positive because the histology will likely be benign. To address correctly this issue, a strict correlation should be performed in patients treated with radical prostatectomy. Our own results (unpublished data) indicate that approximately 5% of TB misses the area accurately detected with Mp-MRI and clearly authenticated as cancer on radical prostatectomy specimen.

- **Mp-MRI negative predictive value**

The negative predictive value of Mp-MRI addresses the probability to miss cancer if a man with non-suspicious Mp-MRI does not undergo biopsy. The difficulty in estimating such issue is that there is no standard verification available. Also, because one of the objectives of a targeted biopsy only strategy should be to avoid over detection of insignificant cancers, studies should be focusing only on significant cancers missed by Mp-MRI. The meta-analysis from Moore et al (13) suggested that about a quarter of biopsy-naive men with no abnormality on Mp-MRI had cancer on standard biopsy, but more importantly that only 2.3% had clinically significant cancer, based on standard biopsy (broadly defined as >5-mm cancer core length and/or any Gleason pattern >3). Standard biopsy are however subjected to significant under staging in approximately 30% of the cases (16, 17), and this percentage may be much higher. Again, studies using a strict correlation with radical prostatectomy specimen are lacking, and the true negative predictive value of Mp-MRI remains unknown.

### b. Accuracy of targeted biopsy

Studies having addressed this issue evaluated TB results in comparison to systematic biopsies. However, because most studies were retrospective, uncontrolled and that standard biopsy was not performed blinded to Mp-MRI results; the impact and level of evidence of their results are low. As summarized in the first chapter of this review, published reports suggested that TB alone (whatever the technique of registration) detect significantly more significant cancers than standard biopsy, while decreasing the detection of insignificant cancers (1, 5, 9). The MURIELLE study is an on-going prospective controlled trial comparing 3 TB using organ-based registration (Koelis® system) versus 12-core systematic biopsy in biopsy-naive patients with a PSA value comprised between 4 and 20 ng/mL and normal DRE, with a unique suspicious area on Mp-MRI (PI-RADS >2). The 2 biopsy protocols are performed by 2 different operators during the same procedure, the operator performing standard biopsy being blinded to the results of Mp-MRI. A total of 90 patients will be included in the next few months, and the primary end-point is cancer involvement on biopsy. Secondary endpoints include cancer Gleason score, cancer maximal length on biopsy cores, as well as procedure time length. Results should be available before the end of the year.

### 3. Value of MRI-TRUS fusion TB for iterative biopsy and follow-up

The value of TB for iterative biopsy is gaining more and more widespread clinical acceptance. Mp-MRI is currently recommended before a second set of biopsies in patients with a persistent biological suspicion of prostate cancer (18). In this setting, TB should be performed to avoid sampling the prostate in the same areas as during the initial biopsy and to under sample unreachable areas (extreme apex and base and anterior portion of the prostate). In patients managed initially with a TB only strategy, evaluation of the gland’s modifications on Mp-MRI would allow a more rational decision making for iterative biopsy. Knowing exactly where primary biopsy was taken within the gland would indeed enable accurate resampling. Last but not least, patients diagnosed with low risk prostate cancer and managed with active surveillance could beneficiate of follow-up TB, that would probably allow a more comprehensive and accurate evaluation of disease status and progression. The value of TB in these clinical settings should be further evaluated in a prospective manner.

### CONCLUSIONS

Integrated US-MR fusion images and MR targeted biopsies appears to be a valuable tool for optimizing prostate cancer detection and follow-up. In a TB only strategy, fewer men could be biopsied overall, with a greater proportion of men diagnosed...
with clinically significant prostate, as well as fewer men "over diagnosed" with clinically insignificant cancer. However, more comprehensive and rigorous clinical research is required before this strategy is ready for widespread adoption. The potential benefit is large and exceeds cancer detection and follow up. In the close future, developing strategies of focal therapy will probably benefit from US-MR fusion technologies, which will enable better staging of the disease at diagnosis, more precise focal treatment and also probably accurate follow-up after treatment.

**BIBLIOGRAFÍA y LECTURAS RECOMENDADAS (“lectura de interés y **lectura fundamental) 


