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Adjusting Our Approach to Multiparametric Magnetic Resonance Imaging-based Targeted Prostate Biopsies: Considerations After the FUTURE Trial

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Technological progress breeds clinical conundrums. While various multiparametric magnetic resonance imaging (mpMRI)-based targeted biopsy (TB) techniques exist to probe clinical suspicion of prostate cancer (PCa), there is no consensus about best practice. Current knowledge comparing TB techniques is limited. To that end, the FUTURE trial in this issue of *European Urology* is much anticipated [1]. We commend the authors for a thoughtful three-armed multicenter randomized controlled trial addressing this very question. The authors predicted that MRI transrectal ultrasound (TRUS) fusion TB (FUS-TB) and in-bore MRI TB (MRI-TB) would have equivalent detection of both PCa and clinically significant PCa (csPCa). The authors also predicted that both techniques would be superior to cognitive registration TRUS TB (COG-TB). This hypothesis was challenged, with the data demonstrating equivalent PCa and csPCa detection by all three techniques. Nonetheless, the FUTURE trial highlights many interesting findings.

First, this study reinforces the indispensable nature of human expertise. Consistent with intuition, it is not surprising that the FUTURE trial found better yield rates for positive biopsy cores by MRI-TB in comparison with FUS-TB and COG-TB. In addition to machine precision, MRI-TB avoids errors associated with co-registration of mpMRI and ultrasound. Yet FUS-TB and MRI-TB were not significantly superior to COG-TB for overall PCa and csPCa detection [1]. Perhaps owing to mpMRI underestimation of tumor volume [2], experts in COG-TB and FUS-TB have a margin of error around the region of interest to achieve outcomes similar to experts relying on MRI-TB. But at the core of successful COG-TB is the requirement for a three-dimensional understanding of mpMRI that can be translated to the ultrasound image. Whether the results from the FUTURE trial can be extrapolated to urologists with less proficiency in mpMRI interpretation is not known.

Second, it is particularly interesting that the FUTURE trial did not demonstrate differences in PCa or csPCa detection rates among men with large prostates, small cancer-suspicious regions, or anterior lesions. One might have hypothesized that MRI-TB would have an advantage in these patients when compared with FUS-TB, and even more so when compared with COG-TB. However, the authors acknowledge that the subgroup analyses must be interpreted with caution as they could reflect the limitations of an underpowered study. For instance, it is established that increasing Prostate Imaging-Reporting and Data System (PI-RADS) v.2 scores correlate with increasing risk of csPCa [3]. It is therefore an unexpected finding that COG-TB csPCa detection is superior for PI-RADS 3 (24%) than for PI-RADS 4 (16%) lesions. Likewise, it is surprising that MRI-TB csPCa detection for PI-RADS 5 lesions was inferior to that via COG-TB and FUS-TB (55%, 64%, and 82%, respectively) [1]. Thus, the small subgroups might have precluded identification of patients for whom one technique or another might be superior. Rather, it can be construed that this study indicates that *overall* there is no clear advantage of one TB technique over another (in expert hands).

Third, it is pertinent to note the mixed transperineal and transrectal biopsy technique implemented in this trial. FUS-TB was performed using a transperineal biopsy technique;

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MRI-TB and COG-TB were performed transrectally [1]. Transperineal techniques have gained more widespread adoption in Europe [4], but are less common in North America (93% transrectal vs 0.4% transperineal) [5]. To the best of our knowledge, there are no comparisons of transperineal and transrectal ultrasound fusion biopsies. There is one comparison of transperineal COG-TB and transrectal FUS-TB in the literature. In a prospective study of 95 men, Pepe et al. [6] showed increased csPCa detection for transperineal COG-TB versus transrectal FUS-TB (93% vs 78%; no *p* value provided). Interestingly, transperineal COG-TB detected significantly more anterior lesions than transrectal FUS-TB (93% vs 25%; $p = 0.001$). However, given the limited literature, it is not clear if the results for transperineal COG-TB reported here in comparison to transrectal FUS-TB can be extrapolated to transperineal FUS-TB. Ultimately, in an effort to reduce the time and cost demands of co-registration systems, as well as the morbidity associated with post-TRUS biopsy sepsis, it would be interesting to investigate PCa detection outcomes via transperineal COG-TB versus transperineal FUS-TB.

Fourth, prospective TB studies generally support the findings of the FUTURE trial. Puech et al. [7] compared COG-TB and FUS-TB in 68 men undergoing both, and found no difference in cancer detection between the techniques (47% vs 53%; $p = 0.16$). However, biopsies were performed by experienced radiologists and may not be generalizable to inexperienced urologists. In a nonrandomized cohort of 156 men, Kaufmann et al. [8] demonstrated a PCa detection advantage for MRI-TB and FUS-TB when compared to COG-TB (51%, 52%, and 29%, respectively; $p = 0.04$) but not for csPCa detection (40%, 36%, and 24%, respectively; $p = 0.27$). Small sample sizes are limitations of the previous two studies. Arsov et al. [9] compared MRI-TB with FUS-TB (with systematic biopsy) in a randomized controlled trial among 210 patients. They found no difference in PCa (37% vs 39%; $p = 0.7$) and csPCa (29% vs 32%; $p = 0.7$) detection rates for MRI-TB vs FUS-TB. However, this study was halted after an interim analysis in which the primary endpoint was not met, thus limiting patient enrollment. Wysock et al. [10] prospectively performed FUS-TB and COG-TB in 125 men, with comparable detection of PCa (32% vs 27%; $p = 0.14$) and csPCa (20% vs 15%; $p = 0.05$). An interesting finding is the improved detection of anterior ($p = 0.03$) and small lesions ($p = 0.04$) on univariate analysis, and of small lesions ($p = 0.005$) on multivariate analysis by FUS-TB. However, these data were obtained from biopsy-naïve (54%) and previously biopsy-negative men (27%) and men on active surveillance (19%). Furthermore, biopsies were obtained transrectally. Operators were also limited to sampling two cores per target, which could have led to a greater chance of missing small targets on COG-TB.

Overall, the findings of the FUTURE trial strengthen our knowledge to better answer how to perform TB in men with a suspicion of PCa in the setting of previous negative biopsies. It carries significant ramifications for clinical practice, particularly in settings without access to MRI-TB or even FUS-TB because of time, technological, and financial burdens. Although we do not yet know the best TB technique for subpopulations of men with anterior lesions, large prostate volume, or small tumor targets, we can use the limitations of the FUTURE trial as a starting point to discuss alternative techniques.

Conflicts of interest: The authors have nothing to disclose.

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