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# Prostate Cancer Diagnosis Using MR/Ultrasound-Fusion Guided Biopsy

## Ending the “Needle in a Haystack” Conundrum?

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### Comparison of MR/Ultrasound Fusion-Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer

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**IMPORTANCE** Targeted magnetic resonance (MR)/ultrasound fusion prostate biopsy has been shown to detect prostate cancer. The implications of targeted biopsy alone vs standard extended-sextant biopsy or the 2 modalities combined are not well understood.

**OBJECTIVE** To assess targeted vs standard biopsy and the 2 approaches combined for the diagnosis of intermediate- to high-risk prostate cancer.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective cohort study of 1003 men undergoing both targeted and standard biopsy concurrently from 2007 through 2014 at the National Cancer Institute in the United States. Patients were referred for elevated level of prostate-specific antigen (PSA) or abnormal digital rectal examination results, often with prior negative biopsy results. Risk categorization was compared among targeted and standard biopsy and, when available, whole-gland pathology after prostatectomy as the “gold standard.”

**INTERVENTIONS** Patients underwent multiparametric prostate magnetic resonance imaging to identify regions of prostate cancer suspicion followed by targeted MR/ultrasound fusion biopsy and concurrent standard biopsy.

**MAIN OUTCOMES AND MEASURES** The primary objective was to compare targeted and standard biopsy approaches for

detection of high-risk prostate cancer (Gleason score  $\geq 4 + 3$ ); secondary end points focused on detection of low-risk prostate cancer (Gleason score  $3 + 3$  or low-volume  $3 + 4$ ) and the biopsy ability to predict whole-gland pathology at prostatectomy.

**RESULTS** Targeted MR/ultrasound fusion biopsy diagnosed 461 prostate cancer cases, and standard biopsy diagnosed 469 cases. There was exact agreement between targeted and standard biopsy in 690 men (69%) undergoing biopsy. Targeted biopsy diagnosed 30% more high-risk cancers vs standard biopsy (173 vs 122 cases,  $P < .001$ ) and 17% fewer low-risk cancers (213 vs 258 cases,  $P < .001$ ). When standard biopsy cores were combined with the targeted approach, an additional 103 cases (22%) of mostly low-risk prostate cancer were diagnosed (83% low risk, 12% intermediate risk, and 5% high risk). The predictive ability of targeted biopsy for differentiating low-risk from intermediate- and high-risk disease in 170 men with whole-gland pathology after prostatectomy was greater than that of standard biopsy or the 2 approaches combined (area under the curve, 0.73, 0.59, and 0.67, respectively;  $P < .05$  for all comparisons).

**CONCLUSIONS AND RELEVANCE** Among men undergoing biopsy for suspected prostate cancer, targeted MR/ultrasound fusion biopsy, compared with standard extended-sextant ultrasound-guided biopsy, was associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer. Future studies will be needed to assess the ultimate clinical implications of targeted biopsy.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00102544

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**The Dutch humanist Erasmus** (1466-1536) once said “In the country of the blind, the one-eyed man is king.” This is not true for prostate cancer’s diagnosis, which remains one of the only blind diagnostic procedures in cancer detection.

The indication for a prostate biopsy is almost always an elevated PSA or an abnormal digital rectal examination. The standard “needle in a haystack” procedure is to perform systematic 10- to 12-core biopsies without knowledge of lesion location in the prostate under transrectal ultrasound (TRUS) guidance. This approach is inefficient, detecting cancers in only 20% to 50% of

cases, of which many are “indolent” and would have been better undetected. In addition, the procedure regularly misses aggressive cancers, thus ironically resulting in both overtreatment and undertreatment.<sup>1</sup> A study conducted in 2007 on autopsy prostates by Haas et al<sup>2</sup> confirmed that even 18-core TRUS-guided biopsies detect cancer in only 53% of prostate cancers.<sup>2</sup> Urologists, the unchallenged doorkeepers of prostate cancer diagnosis, are not in a hurry to solve that conundrum. It took them almost a decade to replace digitally directed biopsies with TRUS-guided biopsies.<sup>3</sup>

Change to an imaging-based approach is limited by a persistent conflict between faith in the standard blind approach and a more Cartesian reasoning about the value and limitation of new techniques, and most especially about multiparametric magnetic resonance imaging (mp-MRI). Prostate MRI is not a new technique, reported as early as 1982, contemporary with TRUS.<sup>4</sup> There has been a worldwide effort to standardize execution and reading of mp-MRI and to validate structured reporting systems, such as PI-RADS (Prostate Imaging Reporting and Data Systems).<sup>5</sup>

A recent systematic review by Schoots et al<sup>6</sup> summarized the benefit of mp-MRI for guiding prostate biopsies. In comparison with standard TRUS-guided biopsies, mp-MRI biopsies increased the detection rate of clinically significant prostate cancer by 10% in men biopsied for the first time, but increased by 54% the detection rate of significant cancers—those requiring treatment—in men with a previous negative finding on biopsy and, more importantly, significantly reduced (by 44%) the detection of clinically insignificant cancers. These are encouraging changes in the diagnostic pathway. Multiparametric MRI is beginning to be incorporated into national and international guidelines such as the 2014 British National Institute for Health and Care Excellence (<https://www.nice.org.uk/guidance>) and European Association of Urology (<http://www.uroweb.org>) (in men with prior negative biopsy findings), and this is likely to occur increasingly over the next few years.

In the January issue of *JAMA*, Siddiqui et al<sup>7</sup> report on a single-institution prospective comparison of standard TRUS and mp-MRI/TRUS fusion-guided biopsy using commercially available software. The authors used a 3-point scale (low, moderate, or high suspicion) to rate lesions, based on consensus between 2 radiologists. The strengths of the trial are its large sample size and the correlation with whole-mount prostatectomy samples. An exact agreement between targeted and standard biopsy was found only in 69% of the patients, but targeted biopsies detected 30% more high-risk cancers (Gleason score,  $\geq 4 + 3$ ) and 17% fewer low-risk cancers (Gleason score, 6 or 3 + 4) with less than 50% of any core containing cancer and fewer than 33% positive biopsy cores. This perfectly addresses the challenge of reducing undertreatment and overtreatment. This study predominantly included patients with previous negative biopsy findings, again supporting this situation as the main current indication of mp-MRI-guided biopsy.

But the center of the debate around mp-MRI remains: there is lack of consensus on reproducibility and of randomized trials. The

article by Siddiqui et al<sup>7</sup> does not report interobserver variability, and the results have not been externally validated, so the conclusion may be only that, *in their hands*, the targeted biopsy procedure outperformed standard biopsies. But will it maintain its accuracy in less expert hands, a prerequisite to convincing urologists to invest in the technology? Multiparametric MRI provides excellent results in excellence centers but highly variable results in the field, with detection rates ranging from 44% to 87%.<sup>6</sup>

If the mp-MRI-targeted biopsy in broader practice is ultimately shown to maintain its improved detection rate, should it replace or complement the standard 12 to 18-core biopsy? In the trial reported by Siddiqui et al,<sup>7</sup> the combined procedure detected 22% more cancers, but 83% of that 22% were low risk. In other words, the combined strategies diagnosed 1 additional high-grade cancer for every 200 men while unveiling 17 additional low-risk cancers, thus challenging the requirement for the standard biopsy altogether. However, abandoning standard biopsies implies not performing biopsies in men with a negative finding on mp-MRI, hence relying heavily on the negative predictive value of that technique. Siddiqui et al<sup>7</sup> do not address that issue: they enrolled only men with at least 1 suspect mp-MRI lesion in the prostate. Again, the final impact will be investigator dependent, considering that negative predictive value varies between trials from 63% to 98%.<sup>8</sup>

Will the findings of Siddiqui et al<sup>7</sup> convince urologists to move away from blinded biopsies? Probably not. The MRI is still seen by many urologists as time-consuming and not cost-effective. Sophisticated computerized MRI-TRUS registration systems may be commercially available, but they come at a very high price and rely on variable technical approaches. Radiologists seem slow to comply with time-consuming standardized guidelines such as the Likert scale and the more descriptive European Society of Urogenital Radiology PI-RADS scoring.<sup>5</sup> Multiparametric MRI and fusion biopsy need investment and training. The wide adoption of mp-MRI for biopsy guidance will rely on standardization and validation of the complex protocols, including quality assurance in mp-MRI acquisition, reading, and reporting; performance and ease of use of the fusion software; and operator skill and experience when performing the biopsy.

The simplest reason for this hesitant attitude is that the quality-controlled, precise, modern image-based biopsy is competing with a practice that takes 5 minutes with a simple ultrasound machine. Change will come, but it will take more time.

#### ARTICLE INFORMATION

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