Letter to the Editor

Omitting the systematic prostate biopsy: ready for prime time?

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Since the introduction of prostate-specific antigen (PSA), widespread screening has facilitated earlier detection of prostate cancer (PCa), which has also led to overdiagnosis and overtreatment. Multiparametric magnetic resonance imaging (mpMRI) have allowed for improved risk stratification of localized PCa. Specifically, mpMRI has enabled cognitive or fusion targeted biopsies (TBx) of concerning Prostate Imaging Reporting and Data System (PI-RADS) 3–5 lesions. Since its inception, TBx have been increasingly utilized, sometimes in the absence of systematic biopsies (SBx). There has been extensive research evaluating the efficacy of TBx and SBx when performed in combination or in isolation for PCa diagnosis.

In the GÖTEBORG-2 trial, the authors demonstrated that omission of SBx for screening and detection of PCa in patients with PSA >3 ng/mL and prebiopsy MRI reduced the diagnosis of clinically insignificant PCa [grade group (GG)1] by half, at the expense of missing 20% of low volume GG2 cancers (1). The diagnosis of GG1 disease was 0.6% in the experimental arm (TBx only), compared to 1.2% in the reference group [relative risk (RR) 0.46, 95% confidence interval (CI): 0.33–0.64, P<0.001]; while clinically significant PCa (csPCa) was detected in 0.9% of the TBx cohort, compared to 1.1% in the reference group (RR 0.81, 95% CI: 0.60–1.10, P>0.05). Only ten patients were diagnosed with csPCa by SBx alone, all of whom had GG2 disease; of these, six were managed with active surveillance (AS), while the remaining four with surgery or radiation. Ultimately, this represented a select experience of PCa screening in a homogenous, Northern European country whose men were screened at relatively low PSA levels only.

A secondary analysis of the TRIO study found that 97% of csPCa was detected via TBx among patients with PI-RADS 5 lesions. SBx only resulted in an additional 2.5% GG ≥2 and 0.8% GG ≥3 diagnosis. Conversely, TBx resulted in only 2% additional detection of csPCa in the PI-RADS 2 cohort. Taken together, the authors note the benefits of combination SBx + TBx appear to be concentrated in men with PI-RADS 3 and 4 lesions and the decision to forgo SBx in PI-RADS 5 and TBx in PI-RADS 2 cohorts will spare 40.1% of men from undergoing a combined biopsy, with only a 1% risk of misdiagnosis among the entire cohort with an abnormal MRI (2).

According to a meta-analysis by Drost *et al.*, pooled data from 25 studies on agreement analyses found a detection ratio of 1.12 (95% CI: 1.02–1.23) for ≥ GG2 disease and 1.20 (95% CI: 1.06–1.36) for ≥ GG3 disease among patients undergoing the MRI pathway (MRI +/– TBx) *vs.* SBx pathway, thus favoring TBx (3). Yet another meta-analysis among biopsy-naïve men by Goldberg *et al.*, similarly demonstrated that TBx results in a significantly higher diagnosis rate of any, high grade and csPCa, while excluding SBx was associated with lower rates of clinically insignificant PCa (4). This seems true even when SBx are indicated after risk stratification with an ultrasound-based risk calculator (5). Among patients with previously negative SBx, TBx also detected more csPCa than SBx, with only 1.3% of csPCa being missed when SBx are omitted altogether (6).

While the diagnostic value of SBx have been heavily

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debated, complete omission of all SBx is still not currently recommended. The diagnostic accuracy of TBx alone has been shown to miss csPCa, which may be secondary to underestimation of tumor volume, suboptimal image fusion, or targeting errors during cognitive inaccuracies (7). Rather, Hagens *et al.* previously described the performance of MRI-directed TBx plus perilesional/regional biopsies to minimize targeting errors, biopsy cores, and grade migration (8,9). A single institutional analysis of 235 men found that this sampling technique would have detected 92/95 (96.8%; 95% CI: 91.0–99.3%) csPCa while reducing diagnosis of insignificant cases by 11/86 (12.8%; 95% CI: 6.6–21.7%) and also reducing the number of biopsy cores (mean difference 5.2; 95% CI: 4.9–5.6, P<0.001) (9). A subsequent meta-analysis of this technique demonstrated that csPCa detection rates were not significantly different when compared to SBx + TBx approaches (RR 0.95, 95% CI: 0.90–1.01, P=0.09) but significantly better when compared to TBx alone (RR 1.18, 95% CI: 1.10–1.25, P<0.001). This technique also used significantly fewer biopsy cores compared to SBx + TBx approach and avoided contralateral SBx altogether (8).

Further methods for improving risk stratification include the adoption of the 2019 International Society of Urological Pathology (ISUP) guidelines for reporting TBx results. They proposed the recommendation of providing an aggregate Gleason score for each suspicious MRI lesion rather than individual TBx core separately, while SBx cores should continue to be reported separately for each location. Benign histologic findings should also be intentionally reported for TBx of suspicious MRI lesions (PI-RADS 4–5) (10).

The omission of SBx has several clinical implications. Patients presenting solely with TBx data may result in discordant and artificially elevated predicted nomogram outcomes, resulting in potentially unnecessary lymph node dissection, which itself is associated with inherent risks. Recent analyses have also demonstrated the impact of regional tumor involvement among serial biopsies performed for AS over time. Higher regional cancer involvement is associated with higher rates of progression to treatment and omitting SBx may alter the ability to interpret longitudinal biopsy results (11). In cases with limited MRI sensitivity, the performance of SBx and detection of low-grade PCa in non-regions of interest may be beneficial in informing surgeons who intend to perform nerve-sparing surgery while decreasing rates of adverse pathologic features (12). While not currently recommended yet, the basis of focal therapy relies on the destruction of localized prostatic lesions reproducibly visualized on imaging. PCa can be multifocal and limitations on mpMRI may result in missed lesions or incomplete ablation of identified tumor. In these cases, SBx may play an important role in patient selection and post-treatment surveillance, especially for men with PCa recurrence after radiation therapy in the absence of metastatic disease (13).

Currently, the clinical conundrum becomes balancing the overtreatment of clinically insignificant versus underdiagnosis of csPCa disease leading to cancer-specific mortality. As the research and technology continues to advance for mpMRI TBx, there may still be value in SBx to be performed in conjunction with TBx to increase diagnostic yield. However, with improved nomograms, additional biomarkers and further trials, SBx may be abandoned altogether.

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Footnote

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