

The role of additional standard biopsy in the MRI-targeted biopsy era

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MANUSCRIPT

Prostate cancer (PCa) is the second most prevalent cancer in men [1], with an aggressiveness ranging from indolent to highly aggressive disease [2].

Historically, the implementation of PSA-based screening strategies has been translated into an increased execution of trans rectal ultrasound based 12-core systematic biopsies (SB), as it still remains the standard of care for the diagnosis of PCa [3].

However, since this diagnostic technique provides non-targeted samples of prostate gland, it is associated with missed cancer diagnosis and misclassification of PCa aggressiveness [4].

These drawbacks could easily lead to under- or over-diagnosis, and most importantly to under- or over-treatment of PCa, with harmful impact over patient health and socio-economic balance in many countries.

The advent of multiparametric magnetic resonance imaging (mp-MRI) of the prostate has been certainly a groundbreaking innovation in this field, allowing a precise localization of suspicious lesions and, subsequently, to perform MRI-targeted prostate biopsies (TB) [5,6].

Notwithstanding many studies have shown an improvement of high grade PCa detection rate (DR) [7] (defined as clinical significant PCa, csPCa) and a better concordance with the whole mount histological specimen in patients who underwent MRI-TB in comparison to SB [8-10], the urologic community still debates whether MRI-TB should be performed in conjunction with or in place of SB, especially in biopsy naïve patients.

Trying to give an answer, Ahdoot et al [11] recently published the results of their study that enrolled 2103 patients who underwent the two biopsy methods. They found that the DR of csPCa of the two techniques considered singularly was higher for TB (13.8% and 20.2% with SB alone and TB alone respectively, $p < 0.05$), and the combination of both allowed an increase in the DR of csPCA of 2.8% with 59 more csPCa diagnoses with an upgrading to a higher grade group that was observed in 458 men (21.8%).

Even if the Authors do not perform a sub-analysis for biopsy naïve patients, they found that more csPCAs were found both with TB and SB at the repeated biopsy (difference, -0.7 percentage points; 95% confidence interval [CI], -3.4 to 2.5 for TB and difference, -0.4 percentage points; 95% CI, -1.7 to 1.1 for SB).

In order to contribute to the debate, we retrospectively analyzed the prospectively collected data from an Italian tertiary center with high experience in MRI-TB.

From March 2014, 1730 patients underwent TB, 336 of whom were biopsy naïve patients who received MRI-TB in addition to SB (Table 1).

All the patients underwent to mp-MRI and the suspicious lesions were classified with the Prostate Imaging-Reporting and Data System (PI-RADS) score v.1 (before 2016), or v.2 and v 2.1 (after 2016 and 2019, respectively).

In about one third of patients, 3T mpMRI without endorectal coil was performed, whilst the remaining patients were scanned on a 1.5T system with endorectal. We would like to underline that in all cases mpMRI was reported by radiologists highly experience in prostate mp-MRI reading.

In our series, TB cores alone had 55.95% of DR vs 63.9% obtained with TB+SB and 40.77% of SB alone.

Considering the cohort of patients who had both TB and SB positive for any cancer (110 patients; 32.7% of the cases) in 91\110 (82.7%) cases the SB confirmed the Gleason Score (GS) of TB; whilst in 14\110 (12.7%) and 5\110(4.5%) cases the SB revealed a downgrading or upgrading respectively.

Moreover, we observed that in 36\110 (32.7%) cases PCa was found contralaterally to the index lesion, among them csPCa was found in 86.1% of the patients (31/36 patients). This finding is particular noteworthy, especially in the view of a subsequent nerve-sparing radical prostatectomy: in fact, 31 patients had csPCa contralaterally respect to the suspicious area at MRI, and this might change the surgical approach.

Focusing on csPCA, this was detected by one or both approaches in 193 cases (57.4%). In order to compare csPCA DR of the two techniques, the McNemar test was used and our analysis revealed a statistically significant difference between the csPCA DR of TB and SB ($p < 0.001$): TB cores identified 179 patients with a csPCA (csPCa DR = 53.27%) compared to 110 using SB (csPCa DR = 32,7%). Only 96 of 193 (28.57%) csPCA were identified by both strategies and 73 tumors (21.7%) were only detected by TB.

Finally, csPCA was identified by SB alone in 14 (4.16%) patients. Among them we found only one Gleason Score 8.

Therefore, we can speculate that in case of a negative TB, the SB allows to detect 4.16% additional csPCa and only in this limited number of cases an active treatment was recommended following the SB findings.

We think that this cohort of patients is the most attractive and debated, because only this 4.16% had a real benefit by the addition of SB cores.

In order to find the proportion of patients deserving SB, a multivariate analysis assessing the association between pre-biopsy parameters and detection of cancer by SB was performed.

This analysis, weighted for lesion's location (peripheral zone or transitional zone), considered five variables: prostate specific antigen (PSA), digital rectal examination, lesion diameter (mm), number of TB samples and PI-RADS score (divided in <3, 3, 4, or 5).

PI-RADS score 4 (OR: 3.90; CI 95% from 1.73 to 11.6; $p=0.014$) and small lesions (OR: 0.85; CI 95% from 0.12mm to 1.07mm; $p=0.035$) seemed to be predictive of positive SB only for PCa.

A possible reason could be found in the more challenging setting for TB to correctly identify small lesions, where the value of SB could be relevant for detect PCa.

In order to better explore this relationship, we tried to identify a cut-off for lesion dimension predicting the presence of PCa in case of negative TB. The most performing model was achieved using the limit of 10 mm ($p=0.012$) with OR 0.13 (CI 95% from 0.08 to 2.20).

Due to the low sample size of csPCa revealed with SB only (14 patients), the multivariable analysis found a trend in favor of low PSA and PI-RADS 4 as predictive variables, but without reaching statistical significance.

Therefore, according to our experience, it seems reasonable to add SB to TB only in case of small (less than 10 mm) but high-suspicious lesions (PI-RADS 4), aiming to reduce the number of SB cores, that have a low probability of clinically impacting a patient's care.

In conclusion, in the current precision medicine era, we think that the addition of SB to TB should be thoroughly investigated, comparing the outcomes of patients undergoing TB and SB with TB only.

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TABLE

Contingency Tables

MRI-TB	SB			Total
	Clinically significant	Clinically insignificant	No Ca	
Clinically significant	96	10	73	179
Clinically insignificant	0	4	5	9
No Ca	14	13	121	148
Total	110	27	199	336

McNemar Test

	Value	df	p
χ^2	53.6	3	< .001
N	336		

Table 1: Contingency table and McNemar test between MRI-TB and SB for cancer detection