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ORIGINAL PAPER

MRI/US fusion prostate biopsy in men on active surveillance: Our experience

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Summary *Aim: The upgrading or staging in men with prostate cancer (PCA) undergoing active surveillance (AS), defined as Gleason score (GS) ≥ 3+4 or more than 2 area with cancer, was investigated in our experience using the software-based fusion biopsy (FB)*

Methods: We selected from our database, composed of 620 biopsies, only men on AS according to criteria of John Hopkins Protocol (T1c, < 3 positive cores, GS = 3+3 = 6). Monitoring consisted of PSA measurement every 3 months, a clinical examination every 6 months, confirmatory FB within 6 months and then annual FB in all men. The suspicious MRI lesions were scored according to the Prostate Imaging Reporting and Data System (PI-RADS) classification version 2. FB were performed with a transrectal elastic free-hand fusion platform. The overall and clinically significant cancer detection rate was reported. Secondary, the diagnostic role of systematic biopsies was evaluated.

Results: We selected 56 patients on AS with mean age 67.4 years, mean PSA 6.7 ng/ml and at least one follow-up MRI-US fusion biopsy (10 had 2 or 3 follow-up biopsies). Lesions detected by MRI were: PIRADS-2 in 5, PIRADS-3 in 28, PIRADS-4 in 18 pts and PIRADS-5 in 5 patients. In each MRI lesion, FB with 2.1 ± 1.1 cores were taken with a mean total cores of 13 ± 2.4 including the systematic cores. The overall cancer detection rate was 71% (40/56): 62% (25/40) in target core and 28% (15/40) in systematic core. The overall significant cancer detection rate was 46% (26/56): 69% (18/26) in target vs 31% (8/26) in random cores.

Conclusions: The incidence of clinical significant cancer was 46% in men starting active surveillance, but it was more than doubled using MRI/US Target Biopsy 69% (18/26) rather than random cores (31%, 8/26). However, 1/3 of disease upgrades would have been missed if only the targeted biopsies were performed. Based on our experience, MRI/US fusion target biopsy must be associated to systematic biopsies to improve detection of significant cancer, reducing the risks of misclassification.

KEY WORDS: *Fusion Biopsy; MRI-US guided Fusion Biopsy; Prostate Cancer; Active Surveillance.*

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INTRODUCTION

Active surveillance (AS) is currently the most rapidly growing management strategy for men with low risk *prostate cancer* (PCA). Aim of AS is to defer or avoid treatments preventing the side effects after active treatments (urinary incontinence and erectile dysfunction) (1). Biopsy criteria for AS vary from one protocol to another: in the original AS was offered only for men with small *Gleason score* (GS) 3+3 = 6 PCA according to Epstein criteria of indolent PCA (2-3), but now in few programs the criteria include men with more extensive GS 3+3 = 6 lesions and even some with GS 3+4 (5).

Upgrading beyond the low-risk cancer found initially has been reported in 35-45% during the first year of follow-up using *systematic biopsies* (SB) (6, 7). Early disease upgrading likely indicates that the initial biopsy findings were inaccurate therefore a more accurate characterization of prostate pathologic findings from the beginning of AS (and during follow-up) would be desirable. Magnetic resonance imaging and MRI-US *fusion biopsy* (FB) has been shown to help characterizing pathologic findings more accurately than SB, leading to improved detection of significant PCA. Use of this new biopsy method has not yet fully evaluated among men undergoing active surveillance (7-9). We present our experience using MRI-US FB in men undergoing AS of PCA.

MATERIALS AND METHODS

This retrospective single center study included 620 consecutive patients who underwent FB between May 2016 and January 2019. We selected from our database only patients on AS. All patients had at least one suspicious lesion at mpMRI, that were performed in different centers as it often happens in community setting without a central review. The suspicious lesions were scored according to the PI-RADS classification v.2. FB were performed with *Koelis*™ system (*Koelis, Meylan, France*), using *Koelis Trinity*™ platform.*Koelis*™ system creates a precise and highly detailed 3D map of the prostate integrating 3D ultrasound, elastic fusion and *Organ-Based Tracking*®. All the biopsies considered in the study were performed with a transrectal approach, as reported in our initial experienceby 3 experienced urologists dedicated to FB (10). Biopsy were performed and specimens collected according to Italian guidelines (11). PCA was considered clinically significant in case of findings of

No conflict of interest declared.

Figure 1.
Fusion + systematic biopsy in a patient on Active Surveillance: 3 targets on a PIRADS 3 lesion in TZa right middle gland and 13 random cores avoiding the previous tracks (blue cores). Results: 2 positive cores GS 3+3 = 6 on target lesion, AS was continued.

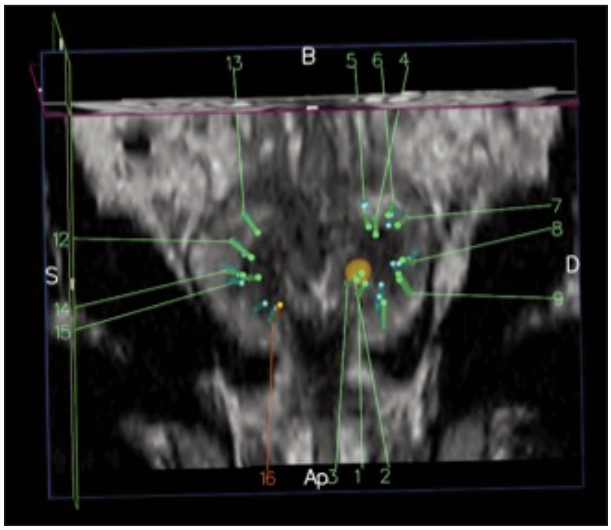
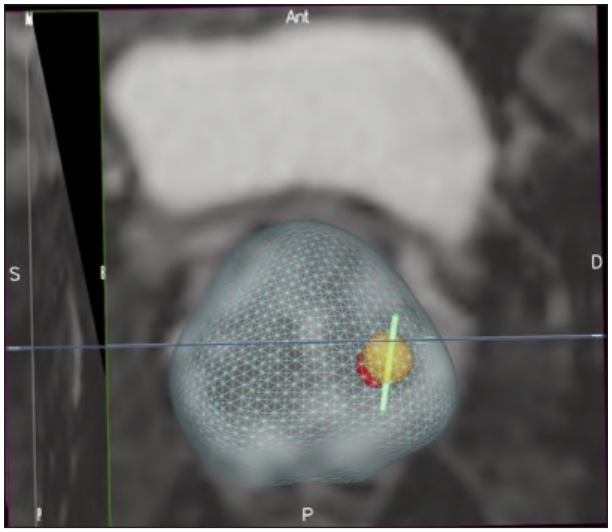


Figure 2.
Anterior-posterior view shows the target core inside the anterior TZ PIRADS 3 lesion at MRI.



Gleason score > 6, or more than 2 cores of Gleason score 6 (or more than 1 core outside the target) as suggested by criteria of many AS protocols. The overall and clinically significant*cancer detection rate* (oCDR, cs CDR) of *Koelis*™ system was obtained. Secondary the diagnostic role of additional SB was evaluated (Figures 1-3).

Results

We selected from our database 56/620 patients on AS with at least 1 follow-up FB. The characteristics of the 56 patients (summarized in Table 1) were: mean age 67.4 years (CI ± 8.8); mean PSA 6.7 ng/ml ± 3.1; mean prostate volume 49.2 ± 21 ml. Lesions detected by MRI: PIRADS 2 = 5 pts; PIRADS 3 = 28 pts; PIRADS 4 = 18 pts; PIRADS 5 = 5 pts. 46 pts had only 1 confirmatory FB, 7 pts had 2 follow-up FB, 3 pts had 3 follow-up FB. Mean cores from each MRI target lesion were 2.1 ± 1.1; mean total cores were 13 ± 2.4. Overall PCA detection rate was 71% (40/56); overall significant PCA (Gleason Score > = 3+4) detection rate was = 46% (26/56); PCA in target core = 62% (25/40); PCA in random core = 28% (15/40); significant PCA in target cores = 69% (18/26); significant PCA in systematic core = 31% (8/26) (as summarized in Table 2).

Figure 3.
Confirmatory biopsy in a 54 yo patient on AS: Fusion biopsy (6 target and 6 sistematyc cores) was PCA positive in 3/6 cores (GS 4+3 = 7). Patient undergone to RARP (Final pathology confirmed a GS = 4+3 = 7 pT2R0N0).

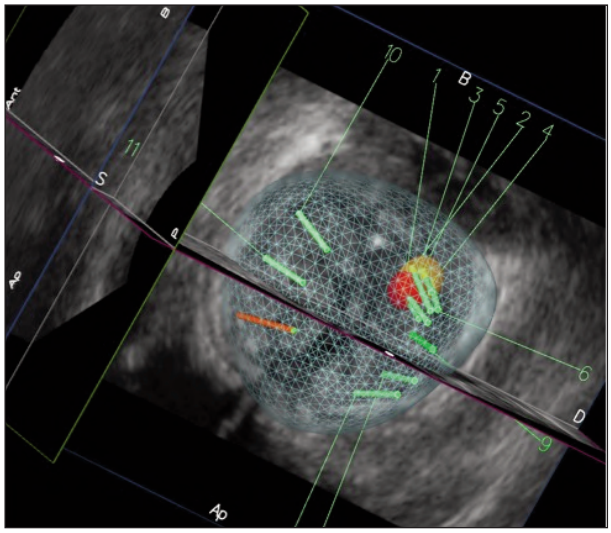


Table 1.
Characteristics of the patients.

Number of patients	56
Age (years), mean (CI)	67.4 ± 8.8
PSA (ng/ml), mean (CI)	6.7 ± 3.1
Prostate volume (ml), mean (CI)	49.2 ± 21
PIRADS of targets (maximum score in case of multiple targets)	
PIRADS 2	5
PIRADS 3	28
PIRADS 4	18
PIRADS 5	5
Mean target cores	2.1 ± 1.1
Mean total cores	13 ± 2.4

Table 2.
Results.

Characteristic	Number
Overall PCA detection rate	71% (40/56)
Significant PCA detection rate	46% (26/56)
PCA detected in target cores	62% (25/40)
PCA in detected in systematic cores	28% (15/40)
Significant PCA detected in target cores	69% (18/26)
Significant PCA detected in systematic cores	31% (8/26)

Discussion

Among the devices used for FB, *Koelis™* is supported by severalrobust evidences (12-14), showing a CDR ranging from 48% to 80%.

We compared our results with *Nassiri et al.* (15), who analyzed 259 men (196 with GS 3+3 and 63 with GS 3+4) who were diagnosed by MRI/US FB (period 2009-2015) and who underwent subsequent FB for as long as 4 years of AS: 63% of men with GS 3+4 were upgraded by the third surveillance year, compared with 18.0% of men with initial GS 3+3 ($p < 0.01$). Moreover, 97% of all upgrades (32/33) occurred within an MRI-visible or a tracked site of tumor, rather than a previously-negative systematic site. *Jayadevan et al.* (17) analyzed men with a new diagnosis of *Gleason grade Group* (GG) 1 PCA (period 2009-2017). The initial diagnostic biopsy was performed by various methods in community settings and within one year from diagnosis, all the men underwent confirmatory FB. Confirmatory biopsy and all follow-up biopsies were performed using a MRI-guided biopsy system. The end point was a finding of at least GG3 disease during follow-up, which then excluded those patients from active surveillance. Of 332 patients in the total cohort of AS, 114 had normal findings on confirmatory biopsy, 175 had GG1 disease, and 43 had GG2 disease. There were 39 patients (11.7%) with upgrading to at least GG3 during the study period with 43% of upgraded cases detected only by *target biopsies* (TB) and 46% d only by SB. Thus, if only one biopsy method was implemented, at least 43% of disease upgrades would have been missed. Similar findings were seen in Improvement in the Detection of Aggressive Prostate Cancer by Targeted Biopsies Using Multiparametric MRI Findings (MRI-FIRST) and the *Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer* (PAIRED-CAP) trials (17, 18).

An analysis of patients undergoing AS by *Frye et al.* (19) at the *National Cancer Institute* also found that the combination of SB and TB should be used during AS follow-up, given that only 30% of pathologic disease upgrades were identified by SB alone.

The efficacy of the combination of both biopsy techniques has been recently confirmed a by *Klots et al.* (20) and *Ma et al.* (21).

In order to reduce side effects of systematic biopsy, several non-invasive strategies has been proposed (22).

The PSA-density, as supported by *Roscigno et al.* (23), was used with a cut-off ≥ 0.20 ng/mL to improve the predictive accuracy of mpMRI results for reclassification of patients in AS, whereas a PSAD value < 0.10 ng/mL identifies a lower risk of harboring clinically significant cancer. Nowadays, the combination of target and SB represents the standard for patients on AS; our study strengthens this recommendation, showing that additional random cores improved the overall CDR of 28% and clinically significant CDR of 31%.

Conclusions

FB represents a useful tool to address many of the limitations of contemporary systematic biopsy. According to most recent evidences and our experience, we believe that MRI/US fusion biopsy improve overall cancer detection rate, clinical significant cancer detection rate and risk stratification among men on active surveillance. Our data suggest that confirmatory and follow-up fusion biopsies with MRI guidance when associated to SB provide a more accurate risk assessmentin order to reduce the oncological risks of AS.

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