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ORIGINAL PAPER

Confirmatory transperineal saturation prostate biopsy combined with mpMRI decrease the reclassification rate in men enrolled in Active Surveillance: Our experience in 100 men submitted to eight-years scheduled biopsy

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Summary ***Introduction: The reclassification rate for clinically significant prostate cancer (csPCa) in men enrolled in Active Surveillance (AS) as been prospectively evaluated.***
Patients and methods: One hundred patients with very low risk PCa underwent after 8 years a scheduled transperineal prostate biopsy (SPBx = 20 cores) combined with additional mpMRI/TRUS fusion biopsies (4 cores) of lesions PI-RADS scores ≥ 3. All the patients, after initial diagnosis, previously had mpMRI evaluation combined with transperineal saturation prostate biopsy (confirmatory and 3-year scheduled biopsy). Risk reclassification at repeat biopsy triggering the recommendation for active treatment was defined as over 3 or more than 10% of positive cores, Gleason score > 6/ISUP Grade Group ≥ 2, greatest percentage of cancer (GPC) > 50%.
Results: Multiparametric MRI was suspicious (PI-RADS ≥ 3) in 30 of 100 cases (30.0%); 70 (70.0%) vs. 20 (20.0%) vs. 10 (10.0%) patients had a PI-RADS score ≤ 2 vs. 3 vs. 4, respectively. Two (2.0%) patients with PI-RADS score 3 and 4 were upgraded (ISUP Grade Group 2); SPBx and MRI/TRUS fusion biopsy diagnosed 100% and 0% of csPCa, respectively.
Conclusions: Transperineal SPBx combined with mpMRI at initial confirmatory biopsy allow to select an high number of men at very low risk of reclassification during the AS follow up (2.0% of the cases at 8 years from diagnosis); these data could be useful to reduce the number of scheduled repeated prostate biopsy during the AS follow up.

KEY WORDS: *Saturation biopsy; Active surveillance; Targeted prostate biopsy; Confirmatory prostate biopsy.*

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INTRODUCTION

Active surveillance (AS) is an alternative (1-3) to radical treatment of low-risk *prostate cancer* (PCa) reducing the risk of overtreatment (50% of the cases) (1) and allowing a strict monitoring over time by scheduled clinical evaluations. *Multiparametric magnetic resonance imaging* (mpMRI) and mpMRI/TRUS (transrectal ultrasound) fusion targeted biopsy have improved systematic biopsies in the diagnosis of *clinically significant PCa* (csPCa) (4, 5), reducing the reclassification rate during the follow up of men in AS. Although the timing to perform confirmatory biopsy has been established within 12 months from initial diagnosis, there are no definitive data regarding the number of systematic needle cores (extended or saturation biopsy) and the best procedure to diagnose all the csPCa reducing the number of scheduled biopsies.
In our study, the reclassification rate for csPCa at 8-year scheduled transperineal biopsy has been prospectively evaluated in men enrolled in AS protocol.

MATERIALS AND METHODS

From May 2013 to September 2017, 160 patients aged between 52 and 73 years (median age 63) with very low risk PCa were enrolled in an AS protocol. After institutional review board and ethical committee approval were granted, informed consents were obtained from all participants included in the study. Presence of the following criteria defined eligibility: life expectancy greater than 10 years, clinical stage T1C, PSA below 10 ng/ml, *PSA density* (PSAD) ≤ 0.20, ≤ 2 unilateral positive biopsy cores, Gleason score 6/*International Society of Urologic Pathology* (ISUP) *Grade Groups* (GG) 1 (6), maximum core percentage of cancer (GPC) ≤ 50% (7). All the patients six months after the PCa diagnosis underwent pelvic mpMRI 3.0 Tesla evaluation before confirmatory transperineal saturation prostate biopsy (SPBx; range: 24-32 cores); the procedure was performed with the use of a GE Logiq P6 ecograph (*General Electric; Milwaukee, WI*) supplied with a bi-planar trans-rectal probe (5-7.5 MHz) using a tru-cut 18 gauge needle (*Bard; Covington, GA*) under sedation and antibiotic prophylaxis (8, 10). All mpMRI examinations were performed using a 3.0 Tesla scanner, (*ACHIEVA 3T; Philips Healthcare Best, the Netherlands*) equipped with surface 16 channels phased-array coil placed around the pelvic area with the patient in the supine position; multiplanar turbo spin-echo *T2-weighted* (T2W), axial *diffusion weighted imaging* (DWI) and axial *dynamic contrast enhanced* (DCE) were performed for each patient.
The mpMRI lesions characterized by *Prostate Imaging Reporting and Data System* (PI-RADS) version 2 scores ≥ 3 were considered suspicious for cancer and submitted to four targeted cores; two radiologists blinded to pre-imaging clinical parameters evaluated the mpMRI data sepa-

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rately and independently;i moreover, one urologist with more than 25 years of experience performed the biopsy procedure. The data were collected following the *Screening Tool to Alert to Right Treatment* (START) criteria (9). At confirmatory biopsy 43/160 (26.8%) were upgraded; conversely, the 117 patients who met clinical criteria to continue AS protocol were submitted every six months to PSA, PSAD and clinical evaluation. At three years from diagnosis of cancer (range: 24-30 months), also in the presence of stable clinical parameters, the remaining 110/117 men enrolled in AS (7 men abandoned the protocol) underwent scheduled repeated SPBx combined with mpMRI/TRUS fusion guided-biopsies of suspicious lesions with PI-RADS ≥ 3 (4 targeted fusion cores) (11) and 5.4% of them were upgraded. The Clavien-Dindo grading system for the classification of biopsy complications was used (12).

During the entire follow up 11/160 (6.8%) men autonomously decided to leave the AS protocol (other 4 men abandoned the protocol after 3-years follow up); on the contrary, after 8 years from the initial diagnosis the remaining 100 patients who were not upgraded at previous follow up visits, again underwent scheduled SPBx (20 cores) combined with mpMRI/TRUS fusion biopsies (4 cores) in the presence of lesions with PI-RADS score ≥ 3.

Risk reclassification at repeat biopsy, triggering the recommendation for active treatment, was defined as over 3 or more than 10% of positive cores, Gleason score > 6/ISUP Grade Group ≥ 2, greatest percentage of cancer (GPC) > 50%. Patients being reclassified underwent definitive treatment (radical prostatectomy or external radiotherapy).

Results

Clinical parameters of the 100 patients included in the AS protocol who underwent repeated prostate biopsy are listed in the Table 1; median PSA value increased 1.3 ng/ml (range: 0-2.2 ng/ml) from time of diagnosis to 8-year scheduled repeat biopsy. Two (2.0%) patients had unfavourable biopsy histology and were reclassified based on upgrading (2 cases = Gleason score 3 + 4/Grade Group 2), number of positive cores (5 and 6 needle positive cores) and GPC (50% and 80%). In detail, all csPCa were located only in the anterior zone of the gland. Of the remaining 98 (98%) patients, 70 (70.0%) were found to have very low-risk PCa and in 28 (28.0%) cancer was absent (normal parenchyma); PCa was located in the periphery in 48 (48.0%) cases and in the anterior zone in 22 (22.0%) cases and all the 98 patients continued AS. Multiparametric MRI was suspicious (PI-RADS ≥ 3) in 30 of 100 cases (30.0%); 70 (70.0%) *vs.* 20 (20.0%) *vs.* 10 (10.0%) patients had a PI-RADS score ≤ 2 *vs.* 3 *vs.* 4, respectively. In detail, the PIRADS score in the 2 men reclassified was equal to 3 in one case (50%) and 4 in the other case (50%). High level of concordance in the diagnosis of PI-RADS score between the two radiologists was found (*Cohen's Kappa 0.85*). None of the patients had significant complications (only Clavien-Dindo grade I) resulting from the prostate biopsy, requiring hospital admission; SPBx and MRI/TRUS fusion biopsy diagnosed 100% and 0% of csPCa, respectively. Finally, all the men reclassified underwent external hypofractionated radiotherapy (13).

Table 1.
Clinical parameters of the 100 men enrolled in the Active Surveillance protocol who underwent scheduled eight-years prostate biopsy.

Median PSA (range)	6.8 ng/ml (2.1-11.3 ng/ml)
Median PSA D (range)	0.12 (0.07-0.18)
DRE	negative
mpMRI	PI-RADS score ≤ 2 = 70 cases; 3 = 20 cases; 4 = 10 cases
Gleason score	6 (3 + 3)
ISUP Grade Group	GG1
GPC (range)	20% (5-50%)
Prostate weight (range)	58 grams (30-110 grams)

PSA: prostate specific antigen; PSAD: PSA density; DRE: digital rectal examination; mpMRI: multiparametric magnetic image resonance; PI-RADS: Prostate Imaging Reporting and Data System; GPC: greatest percentage of cancer; ISUP: International Society of Urologic Pathology.

Discussion

The estimated treatment-free probability at 5, 10 and 15 years from diagnosis of patients enrolled in AS protocol with GG1 PCa has been reported equal to 76, 64 and 58%, respectively (14); on the other hand, more than one-third of patients, during follow up, are reclassified (i.e., PCa upgrading and/or increase in disease extent or patient preference) and submitted to curative treatment (15). In detail, the confirmatory biopsy within one year from diagnosis upgrade the highest number of patients; in particular, the transperineal template biopsy upgrade about 38.0% of patients (16). A lot of studies reported on criteria of patient selection and follow up policies of men enrolled in AS protocol: type and timing of imaging, frequency of repeat prostate biopsies, use of PSA density and kinetics, genetics biomarkers, use risk calculators, and frequency of clinical follow-up (17-23). Although mpMRI is strongly recommended in patients enrolled in AS protocols (24), at present, systematic prostate biopsies should be always combined with targeted fusion biopsy due to the false negative rate of mpMRI (25-27); moreover, the number of targeted-fusion biopsy (in the presence of PI-RADS ≥ 3) that should be obtained in addition to systematic prostate biopsy in men enrolled in AS protocols (8) has not been established (28). In fact, an accurate biopsy histology could reduce the risk of reclassification allowing to postpone scheduled prostate biopsies in favour of clinical parameters evaluation reducing, at the same time, the complications rate following repeated biopsies (i.e., risk of sepsis and hospitalization) (29). At the same time, an adequate number of needle cores allows to select patients with high volume GG1 PCa at risk of reclassification during follow up (33.4% of the cases) (30). In this respect, the number of systematic and/or targeted biopsy cores is an independent predictor for selection of patients with unfavourable characteristics for AS (31-35). On the other hand, a relevant critical point remain the adherence of patients to scheduled AS follow up; in fact, the estimated drop out to the execution of repeated prostate biopsy at 1 *vs.* 4 *vs.* 7 years from initial diagnosis is equal to 11 *vs.* 30 *vs.* 29%, respectively (3); therefore, the *European Association of Urology* (EAU) guidelines strongly recommend to perform repeat biopsy in the presence of clinical suspicion of PCa progression (i,e., PSAD evaluation, progression on mpMRI) instead to

repeat biopsies at scheduled times that, anyway, are suggested every three years (36, 37). Finally, pathologic parameters play a critical role in identifying appropriate candidates for AS; these findings need to be reproducible and consistently reported by pathologists (38-40).
In our series, 2/100 (2.0%) men were reclassified based on upgrading (*Gleason score 7/ ISUP Grade Group 2*), number of positive cores (5 and 6 positive cores) and GPC (50% and 80%); SPBx and mpMRI/TRUS fusion biopsy detected 100 vs. 0% of csPCa. In definitive, the execution of SPBx plus mpMRI at initial confirmatory biopsy allowed to select an high number of men at a very low risk of reclassification (from GG1 to GG2) during the AS follow up (5.4% and 2.0% of the cases at respectively 3 and. 8 years from diagnosis) (11); these data could be useful to reduce the number of scheduled repeated prostate biopsy during the AS follow up.
Regarding our results, some considerations should be made. First, in our series there was not a control arm of men submitted to systematic 12 cores prostate biopsy; therefore, the data obtained have been compared with the literature results. Second, the results were evaluated on biopsy specimens and not on the entire prostate gland. Third, the negative histology of the 9 patients with PI-RADS score 4 should be evaluated during the follow up. Finally, a large number of men including a longer follow up are needed to confirm our results.

Conclusions

Transperineal SPBx combined with mpMRI at initial confirmatory biopsy allow to select an high number of men at very low risk of reclassification during the AS follow up (2.0% of the cases at 8 years from diagnosis); these data could be useful to suggest reducing the number of scheduled repeated prostate biopsy during the AS follow up.

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