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Oncological Outcomes in Men With Favorable Intermediate Risk Prostate Cancer Enrolled in Active Surveillance

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Abstract. *Background/Aim: To evaluate the long-term oncological outcomes in men with intermediate risk prostate cancer (PCa) enrolled in active surveillance (AS). Patients and Methods: From April 2015 to December 2022, 30 men with Gleason score 3+4/ISUP Grade Group2 (GG2), greatest percentage of cancer (GPC) ≤50%, Gleason pattern 4 ≤10%, ≤3 positive biopsy cores were enrolled in AS. All patients underwent confirmatory transperineal saturation biopsy (SPBx: 20 cores) 12 months from diagnosis plus multiparametric magnetic resonance (mpMRI) evaluation. At the last follow-up, 68Ga prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/computed tomography (CT) was added: lesions with PIRADS score ≥3 and/or standardized uptake value (SUVmax) >5 were submitted to four targeted cores. Results: Three out of 30 (10%) men with GG2 PCa were reclassified at confirmatory biopsy. At the last follow-up (median 5.2 years), only 2 of 27 (7.4%) men were reclassified and 23/30 (76.6%) continued AS. Conclusion: Men with favorable GG2 PCa enrolled in AS have good long-term oncological results. The use of selective criteria (i.e., SPBx, mpMRI, PSMA PET/CT) reduces the risk of reclassification.*

Prostate cancer (PCa) is the most prevalent tumor among men and has a considerable impact on morbidity and mortality worldwide with more than 1.4 million new diagnoses in 2020 and 375,000 associated deaths worldwide (1). With an aging population, the number of patients with less aggressive and localized PCa has increased by the use of prostate-specific antigen (PSA) screening; although, the risk to detect not clinically significant PCa (Gleason score 6/ISUP Grade Group 1) is decreased following the introduction of multiparametric magnetic resonance (mpMRI) in clinical practice (2, 3). As a result, many indolent PCas are diagnosed and conservatively treated using the Active Surveillance (AS) protocol because definitive treatments, such as radical prostatectomy (RP) and radiotherapy, can decrease one's quality of life (QOL) in terms of urinary, sexual, and bowel functions without an increased survival rate. The management and monitoring of men enrolled in AS has improved by the use of mpMRI and transperineal prostate biopsy, and in clinical trials, by the genetic counselling and prostate-specific membrane antigen (PSMA) positron-emission tomography/computed tomography (PET/CT) evaluation (4, 5).

Recently, men with intermediate risk PCa characterized by Gleason score 3+4/International Society of Urologic Pathology (ISUP) Grade Group (GG) 2 with Gleason pattern 4 ≤10%, a number of positive cores ≤3 with a greatest percentage of cancer (GPC) ≤50 have been considered suitable for AS with good long-term results in terms of overall survival and clinical progression (6, 7).

We here report the long-term oncological outcomes of men with intermediate favorable PCa risk enrolled in the AS protocol.

Patients and Methods

From May 2013 to December 2022, 200 men aged between 52 and 73 (median age 63) with a very low risk PCa were enrolled in the AS protocol. After institutional review board and ethical committee approval were granted, informed consents were obtained from all participants included in the study. The presence of the following criteria defined eligibility: life expectancy greater than 10 years, clinical stage T1C, PSA below 10 ng/ml, PSA density (PSA-D) <0.20, ≤3 positive biopsy cores, Gleason score 6/ISUP GG1, and maximum core percentage of cancer (GPC) ≤50% (8). All the patients 12 months after the PCa diagnosis underwent mpMRI evaluation and confirmatory transperineal saturation prostate biopsy (SPBx: 20 cores): 45/200 (22.5%) men were upgraded, and 12/200 (6%) men autonomously decided to leave the AS protocol (9, 10).

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Table I. *Initial clinical parameters of 30 men enrolled in the Active Surveillance protocol with favourable intermediate risk prostate cancer.*

Clinical and biopsy findings	Gleason score 3+4/ISUP GG2 30 patients
Median PSA	5.8 (range=4.5-10.5 ng/ml)
Median PSA density	0.14 (range=0.10-0.20)
Median GPC	40% (range=10-50%)
Median number of positive cores	2
Percentage of Gleason score 4 in single core	5%
mpMRI	30
PI-RADS score ≥3	14 (46.7%)

ISUP GG: International Society of Urological Pathology Grade Group; mpMRI: multiparametric magnetic resonance imaging; PSA: prostate specific antigen; GPC: greatest percentage of cancer; PSMA: Prostate specific membrane antigen; PI-RADS: Prostate imaging reporting and data system; PET/TC: positron emission tomography/computed tomography.

Table II. *Clinical parameters of 23 men enrolled in the Active Surveillance protocol with intermediate risk PCa at median follow up of 5.2 years (range=3-8 years).*

Clinical and biopsy findings	27 patients Gleason score 3+4/GG2
Median PSA	6.8 (range=4.2-11.5 ng/ml)
Median PSA density	0.14 (range=0.10-0.18)
mpMRI	23
PI-RADS score ≥3	13 (56.5%)
68Ga-PSMA PET/CT	23
Median SUV max	5.8 (range=4-12)
suspicious for PCa (SUV max ≥5)	8 pts (34.8%)

ISUP GG: International Society of Urological Pathology Grade Group; mpMRI: multiparametric magnetic resonance imaging; PSA: prostate specific antigen; GPC: greatest percentage of cancer; PSMA: prostate specific membrane antigen; PI-RADS: prostate imaging reporting and data system; PET/TC: positron emission tomography/computed tomography; SUV: standardized uptake value.

At a median follow-up of 6.1 years (range=12-120 months) 139/200 (69.5%) very low risk patients continued the AS protocol.

From April 2015 to December 2022, a subset of 30 men with intermediate risk PCa adequately informed, accepted to be enrolled in the AS protocol; the presence of the following biopsy histology parameters defined eligibility: Gleason score 3 + 4/ISUP GG2, GPC ≤50%, Gleason pattern 4 ≤10%, and ≤3 positive biopsy cores. During the follow-up (median 5.2 years; range=2-8 years), the 30 men with intermediate risk PCa (Table I) underwent the same scheduled protocol adding ^{68}GaPSMA PET/CT to the mpMRI evaluation before last SPBx.

All mpMRI examinations were performed using a 1.5 and 3.0 Tesla scanner equipped with surface 16 channels phased-array coil placed around the pelvic area with the patient in the supine position; the mpMRI lesions characterized by Prostate Imaging Reporting and Data System (PI-RADS) version 2 (4) scores ≥3 were suspected to be cancer (11). PET/CT imaging was performed using a CT-integrated PET scanner (Biograph 6; Siemens, Knoxville, TN, USA); PSMA was prepared with a fully automated radiopharmaceutical synthesis device based on a modular concept (Eckert & Ziegler Eurotope, Berlin, Germany). Images were processed to obtain PET, CT, and PET-CT fusion sections in the axial, coronal, and sagittal planes with a thickness of approximately 0.5 ~ cm; the location of focal uptake on ^{68}Ga-PSMA PET/TC, three-dimensional size, and standardized uptake value (SUVmax) values were reported on a per-lesion basis (12, 13).

All the mpMRI (PI-RADS score ≥3) (10) and ^{68}Ga-PET/TC index lesions (SUVmax ≥5) (4) underwent cognitive targeted cores (mpMRI-TPBx and PSMA-TPBx: four cores) combined with SPBx; the procedure was performed transperineally using a Hitachi 70 Arietta ecograph (Hitachi, Chiba, Japan) supplied by a bi-planar trans-rectal probe under sedation and antibiotic prophylaxis (14).

Results

All the patients with a favorable GG2 PCa risk underwent 12 months after the diagnosis mpMRI evaluation plus confirmatory transperineal SPBx and 3/30 (10%) were reclassified: all the patients had a GG2 PCa characterized by a Gleason 4 pattern <10% with a GPC >50% in two cases (70 and 80%) and in 3/3 cases by a number of positive cores greater than 3 (4 cores in two cases and 5 cores in one case). During the follow-up (median 5.2 years) the men underwent scheduled transperineal SPBx combined with additional mpMRI/TRUS fusion biopsies (4 cores) of lesions with PI-RADS scores ≥3 and 2/27 (7.4%) of them were reclassified: 3 cores involved by Gleason score 4+3/ISUP GG3 with a percentage of cancer GPC of 50%; PSA density was 0.20, PIRADS score 4 and median SUVmax 8.2. The other 25/30 (83.3%) patients continued follow-up and clinical parameters are reported in Table II. Two men autonomously decided to leave the AS protocol. At the last scheduled biopsy, mpMRI and ^{68}PSMA PET/CT showed 14/23 (60.8%) and 8/23 (34.7%) lesions were suspicious for PCa and were submitted to targeted cores combined with SPBx. In detail, mpMRI PI-RADS score resulted in ≤2 *vs*. 3 *vs*. 4 in 10 (43.8%) *vs*. 8 (34.8%) *vs*. 5 (12.4%) men. The average intraprostatic SUVmax and tumor dimension were 4.6 g/ml (range=3.2-19.8 g/ml) and 7.0 mm (range=4-12 mm), respectively. Only 8/23 (34.8%) men had a SUVmax ≥5 (range=5.1-19.8). Moreover, ^{68}Ga-PSMA PET/TC showed two suspicious lesions for metastases in correspondence with the iliac ala and spinal cord, which were not confirmed by MRI evaluation.

Discussion

The estimated treatment-free probability at 15 years from diagnosis of patients with GG1 PCa enrolled in the AS

protocol is equal to 58% (15). At a median follow-up of 15 years, cancer-specific mortality of 1,610 patients with localized PCa (more than one third with intermediate or high-risk disease) was 2.7% irrespective of treatment. Moreover, 24.4% of men enrolled in the AS protocol were alive without any curative treatment (16). Gearman *et al*. (17) reported that 93.9% and 82.6% of 8,095 patients with GG1 or GG2 PCa who underwent RP showed an organ confined disease and the 10-year systemic progression-free survival rate equal was to 99% *vs*. 96.5%, respectively.

AS is endorsed by clinical guidelines as the preferred management strategy for low-risk prostate cancer; the American Urological Association (AUA) Quality (AQUA) Registry Rates report a sharply and consistently increased number of men enrolled in AS from 2014 (26.5%) to 2021 (59.6%) (18). Although favorable GG2 PCa are found to harbor adverse surgical pathology histology in about 25% of the cases (19), a low percentage of Gleason pattern 4 in biopsy is associated, in selected cases, with favorable prostatectomy histology and good oncological outcomes (Table III); men with GG2 cancer combined with Gleason pattern 4 <5% in a biopsy core had a definitive histology similar to patients with GG1 PCa (20). Conversely, the risk of upgrading at definitive histology in men with 1 or 2 cores with Gleason score 3+4 and PSA levels <20 ng/ml is higher in the case of a single core with Gleason pattern 4 >20% (21, 22). Klotz *et al*. (23) reported that candidates with a better prognosis were men categorized as having intermediate-risk disease with a PSA level between 10 and 20 ng/ml, a GG2 disease with a small percentage of Gleason 4 pattern, a negative mpMRI or negative targeted biopsy. Musunuru *et al*. (24) reported that at a median follow-up of 6.7 years among the estimated 15-year metastasis-free survival of 213 patients with GG2 PCa was equal to 84%.

Clinical, genomic, and radiological biomarkers including the Decipher Genomic Classifier, circulating miRNAs and urinary biomarkers, have been reported to improve risk stratification and patient selection (25-29). Regarding the genetic markers, Carter *et al*. (30) reported that *BRCA2* mutations in men enrolled in AS were associated with a higher risk of reclassification. Imaging has improved AS criteria especially in cases of intermediate risk PCa; although mpMRI is strongly recommended in AS, it is not yet practical to omit scheduled prostate biopsy and replace it entirely with mpMRI alone because the non-negligible percentage of false negative rate (31). However, mpMRI combined with other clinical parameters has reduced sampling errors and underdiagnosis during systematic biopsy (32). Huang *et al*. (33) showed that that lower apparent diffusion coefficient (ADC) values of the index lesion are significantly associated with an increased risk of reclassification in men on AS with GG1 PCa (34). Recently, PSMA PET/CT demonstrated good accuracy in the diagnosis of clinically significant PCa being not inferior to mpMRI evaluation (35-37); in fact, SUVmax value has been correlated with PCa aggressiveness (12). Roscigno *et al*. (38) reported that in the presence of negative mpMRI a PSA density higher than 0.20 allowed to diagnose 16% of GG2 PCa; moreover, Saout *et al*. (39) reported that negative mpMRI and PSA density ≤0.10, during follow-up had an excellent negative predictive value for treatment. Dai *et al*. (40) reported in multivariable analysis that age, number of positive cores and perineural invasion in biopsy histology were independent predictors of reclassification. Other studies focused on approaches of prostate biopsy procedure to reduce the risk of upgrading; Zattoni *et al*. (41) reported that transperineal targeted biopsy improves the concordance of biopsy and final histology; in addition, transperineal SPBx reduces the risk of upgrading during AS follow-up (9, 42). Recently, the introduction in clinical practice of digital pathology has improved the accuracy of biopsy histology in selecting men candidates for AS allowing to better identify the percentage of GG2 PCa using the needle core (43).

Table III. *Reclassification rate for men with favorable intermediate risk PCa enrolled in the Active Surveillance (literature data).*

Author	PCa reclassification rate	Follow up (years)	Urologic Center
Klotz *et al*. (46)	25.6%	6.4	University of Toronto
Kirk *et al*. (47)	22.4%	5.6	Canary Prostate Active Surveillance Study
Bohhorst *et al*. (48)	41%	10	PRIAS
Baboudjian *et al*. (49)	31-80.6%	10	Meta-analyses-25 studies 29,673 men

Despite being a noninvasive treatment strategy, AS may subject some patients to active examinations, as it fails to consider the speed of individual disease progression; the use of risk-calculator that includes factors, such as age, PSA level, PSA kinetics, biopsy results, mpMRI findings, and genetic testing may influence the risk classification and selection for each man in AS (44-50).

In our series, only 5/30 (16.6%) men with favorable GG2 PCa were reclassified during the follow-up (median 5.2 years) and 2/30 (6.7%) decided to leave AS; our results demonstrated an accurate selection of the patients by performing transperineal SPBx, mpMRI and, recently, PSMA PET/CT that allowed to continue AS in 23/30 (76.6%) men.

Some considerations should be made regarding our results. First, the number of patients is low, and a greater number of patients should be prospectively evaluated.

Second, the low reclassification rate at confirmatory biopsy of GG2 *vs*. GG1 PCa (16.6 *vs*. 22.5%) could be correlated with the accurate clinical inclusions criteria (*i.e.,* PSA and PSAD values, SPBx) that allowed the diagnosis of small volume GG2 PCa. Finally, a long-term follow-up is needed to confirm oncological outcomes.

In conclusion, men with intermediate favorable GG2 PCa could be enrolled in the AS protocol with good oncological long-term results. The use or selective criteria (SPBx, mpMRI, PSAD, genetic counselling, digital pathology, PSMA PET/CT) could reduce the risk of reclassification during the follow-up.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, P.P.; Methodology, P.P.; Software, P.L.; Validation, P.P., P.L.; Formal Analysis, P.P, P.L.; Investigation, P.P.; Resources, P.P.; Data Curation, P.P., P.L.; Writing – Original Draft Preparation, P.P., P.L.; Writing – Review & Editing, P.P., P.L.; Visualization, P.P, P.L., P.M., F.F.; Supervision, P.P.

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