Active surveillance in males with low-to-intermediate-risk localized prostate cancer: A modern prospective cohort study

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Purpose: To compare the clinical outcome of males with low-risk and favorable intermediate-risk prostate cancer managed within a standardized modern protocol of active surveillance.

Materials and Methods: This was a prospective cohort study with strict and expanded active surveillance criteria in males with prostate cancer. Baseline assessment included multiparametric magnetic resonance imaging (mpMRI), extended systematic biopsy, and software-based MR-targeted biopsy. Follow-up included biannual prostate-specific antigen (PSA) check, mpMRI, and control biopsy once a year for the first 2 years, and afterward mpMRI every 2 years with additional tests as clinically indicated. The primary outcome was the transition rate to active treatment.

Results: A total of 51 patients were included: 17 (33%) and 34 (67%) followed protocols of strict (study arm 1) and expanded (study arm 2) active surveillance criteria, respectively. Median age and PSA were 65 years (IQR, 60–69 years) and 5.3 ng/mL (IQR, 4.5–7.7 ng/mL), respectively. At baseline, a median of 2 (IQR, 1–3) cores were positive out of 13 (IQR, 12–14) cores; 22 males (43%) had visible mpMRI lesions. Eight males (24%) in study arm 2 had Gleason score 3+4. After a median follow-up of 36 months (IQR, 24–48 mo), no patient in study arm 1 compared with 17 patients (33%) in arm 2 underwent active treatment (p<0.0005).

Conclusions: Although expanding eligibility criteria leads to a greater transition rate to active treatment, active surveillance should be contemplated in well-selected males with favorable intermediate-risk prostate cancer as the curability window seems to be maintained.

Keywords: Active surveillance; Magnetic resonance imaging; Prostate cancer

INTRODUCTION

Level 1 evidence shows that active surveillance (AS) is a valid option for males with low-risk prostate cancer (PCa) [1]. Historically, strict criteria have been applied to select males eligible for an AS policy to minimize the risk of missing the
The consequences are twofold: TRUS systematic random biopsy should not be arbitrarily applied to define eligibility for AS since our diagnostic tools are changing but not the disease itself. Prospective studies evaluating the outcome of AS in patients with strict and expanded criteria in patients harboring low to favorable intermediate-risk PCa, respectively. Eligible patients were assigned to two groups according to disease features at baseline strict criteria (study arm 1, or control arm) and expanded criteria (study arm 2, or interventional arm). The eligibility criteria are listed in Table 1. Transition from study arm 1 to study arm 2 or progression within each arm was permitted; it was not an indication for active treatment per se.

1. Design and inclusion criteria

This was a prospective research ethics committee-approved (Cantonal Commission on Ethics in Human Research [CER-VD]) multiple-arm cohort study (approval number: NCT01795365, date of registration: 20/02/2013). Informed written consent was obtained from all study subjects. The aim of this study was to compare the clinical outcome of AS with the use of strict and expanded criteria in patients harboring low to favorable intermediate-risk PCa, respectively. Eligible patients were assigned to two groups according to disease features at baseline strict criteria (study arm 1, or control arm) and expanded criteria (study arm 2, or intervention arm). The eligibility criteria are listed in Table 1. When choosing the upper threshold for cancer burden in biopsy in study arm 2, we fixed the maximum length threshold at 8 mm because this corresponds to the upper relevant lesion diameter suggested within a randomized screening trial [7]. Patients not meeting all the strict AS criteria were assigned to the intervention arm (study arm 2).

2. Follow-up

Both groups underwent identical diagnostic assessment at baseline and follow-up (Table 2). Baseline assessment included prostate-specific antigen (PSA) check, digital rectal examination, mpMRI, and extended random and MR-targeted biopsy. The follow-up included PSA assessment twice a year, mpMRI and control biopsy once a year for the first 2 years, and thereafter mpMRI every 2 years. According to PSA variation or imaging change, additional tests were performed, as clinically indicated. Transition to active treatment was advised in males whose disease progressed beyond the expanded eligibility criteria. Transition from study arm 1 to study arm 2 or progression within each arm was permitted; it was not an indication for active treatment per se.

Table 1. Inclusion criteria for the study arms using strict and expanded criteria

| Inclusion criteria                        | Study arm 1–strict criteria | Study arm 2–expanded criteria |
|------------------------------------------|-----------------------------|------------------------------|
| PSA (ng/mL)                              | <10                         | <15                          |
| Gleason score                            | 3+3=6                       | ≤3+4                         |
| No. of positive biopsies                 | ≤3                          | ≤5                           |
| Maximum cancer burden (mm and % invasion) | ≤3 mm and <50% invasion    | ≤8 mm                        |
| mpMRI PI-RADS score                      | 1–3                         | 4–5                          |

PSA, prostate-specific antigen; mpMRI, multiparametric magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System.
although this was discussed according to the local standard of care in cases of disease progression in males under AS.

MpMRI and the biopsy protocol were standardized. Prostate mpMRI was acquired and interpreted according to the Prostate Imaging Reporting and Data System (PI-RADS) score and was reported by a single expert radiologist. A 3T magnetic field strength with an endorectal coil was used, including T1-weighted sequences, T2-weighted sequences, diffusion-weighted imaging (DWI) with corresponding apparent diffusion coefficient maps, and dynamic contrast-enhanced sequences. Prior to biopsy, all mpMRI data were reviewed in a dedicated uro-radiology meeting where the radiologist annotated all lesions with PI-RADS scores ≥3.

Delineated T2-weighted and DWI sequences were uploaded into the KOELIS Urostation (Koelis, Meylan, France). At the time of biopsy, the prostate contour was defined by using semi-automatic embedded software. A TRUS end-fire probe was used to acquire three-dimensional images using the Samsung Ultrasound UGEO 60 (Samsung Medison, Seoul, Korea). Afterward, axial TRUS images were contoured and elastic-fusion was performed. All patients underwent MR-targeted biopsy with 2 to 4 needles deployed per target followed by 10–12-core standard biopsy. If the MR target was located in the peripheral sextant sampled by standard biopsy, additional random sampling in the same area was omitted. All biopsies were performed by two expert consultant urologists.

When active treatment was prompted, patients were managed as per the standard of care in the local Prostate Cancer Unit. Treatment options were offered as part of a multidisciplinary approach considering relevant clinical criteria as well as the patients’ values. Focal therapy was offered using high frequency focused ultrasound (HIFU) or cryotherapy; radical prostatectomy (RP) was proposed in an open or laparoscopic robotic-assisted fashion; external radiotherapy was proposed by using a standard protocol or a hypofractionated scheme within a recently reported prospective study [8].

The follow-up protocol after active treatment was standardized. Patients who underwent RP or radiotherapy were routinely followed up as recommended by the EAU guidelines. Patients undergoing focal therapy also underwent a standardized follow-up within a prospectively maintained registry; failure of focal therapy was defined as any residual or recurrent clinically significant disease (≥3+4), secondary local treatment, PCa-related death, or transition to metastatic disease.

3. Statistical analysis

The overriding hypothesis of this study was that by using precise tools of assessment at baseline, the transition to active treatment would not differ significantly between the two groups after 6 years of follow-up. The power calculation was adjusted based on the study by Cooperberg et al. [9], which indicated the rates of transition to active treatment as 30% and 35% for patients risk-stratified by random biopsy and followed by active monitoring with the use of low- and intermediate-risk criteria, respectively. With 80% power and a two-sided α level of 5%, the study sample size was 45 patients in each group, allowing an estimated difference of 15% between groups. Considering a 10% dropout rate, the final sample size was 50 patients per group. We estimated a recruitment time of 5 years; the analysis in the present study was performed after this time frame. Group differences in categorical variables and continuous variables were analyzed with chi-square tests and Kruskal–Wallis tests, respectively. The difference in duration of AS between groups was measured by using Kaplan–Meier survival plots. Potential predictors of active treatment were analyzed by univariable and multivariable Cox proportional hazards regression analysis. All statistical tests were two-sided with significance set at a p-value of <0.05. All analyses were conducted with Stata 15 (StataCorp, College Station, TX, USA).

RESULTS

At the time of this analysis (November 2018), 51 patients were enrolled: 17 (33%) had strict and 34 (67%) had expanded criteria. The CONSORT flow diagram is presented in Fig. 1. Clinical and pathologic characteristics of the patients are
Modern prospective study of active surveillance shown in Table 3. The patients’ median age and PSA at diagnosis were 65 years (interquartile range [IQR] 60–69 years) and 5.3 ng/mL (IQR, 4.5–7.7 ng/mL), respectively. A median of 2 cores (IQR, 1–3) were positive out of 13 cores (IQR, 12–14) at baseline. The patients’ age, PSA, and clinical stage were similar between groups. Patients with expanded criteria had more cancer burden at the baseline biopsy in terms of the number of biopsies with cancer, the percentage of biopsies with cancer, the maximum cancer burden in a single core, the total cancer core length, and the maximum cancer core length (MCCL) in a single biopsy. Median follow-up time was 3 years (IQR, 24–48 months).

Overall, 17 patients (33%) underwent active treatment within the study time frame; all of them had been assigned to study arm 2 (p=0.0005; Fig. 2). Median time to active treatment was 12 months (IQR, 6–36 months). Reasons for active treatment were Gleason score progression (n=6, 35%), tumor volume progression (n=7, 41%), mpMRI progression (n =3, 18%), and patient’s decision (n=1, 6%). However, only nine patients experienced progression beyond the expanded AS criteria: seven in terms of cancer burden (>5 positive

### Table 3. Characteristics of the patients included in the study

| Variable                                           | Overall population | Strict criteria (study arm 1) | Expanded criteria (study arm 2) | p-value |
|----------------------------------------------------|--------------------|-------------------------------|---------------------------------|---------|
| Number of patients                                 | 51 (100)           | 17 (33)                       | 34 (67)                         |         |
| Age (y)                                            | 65 (60–69)         | 64 (60–69)                    | 66 (62–69)                      | 0.3     |
| PSA baseline (ng/mL)                              | 5.3 (4.5–7.7)      | 5.2 (3.4–6)                   | 5.6 (4.5–8.1)                   | 0.8     |
| PSA density (ng/mL/cm³)                           | 0.16 (0.1–0.2)     | 0.11 (0.1–0.2)                | 0.18 (0.1–0.3)                  | 0.2     |
| Clinical tumor stage                               |                    |                               |                                 |         |
| cT1a                                               | 7 (14)             | 4 (23)                        | 3 (9)                           | 0.3     |
| cT1c                                               | 39 (76)            | 12 (70)                       | 27 (79)                         |         |
| cT2a                                               | 5 (10)             | 1 (7)                         | 4 (12)                          |         |
| Baseline PIRADS score                             |                    |                               |                                 | <0.01   |
| 1–3                                                | 29 (57)            | 17 (100)                      | 12 (35)                         |         |
| 4–5                                                | 22 (43)            | 0 (0)                         | 22 (65)                         |         |
| Prostate volume (mL)                              | 33 (23–52)         | 33 (20–54)                    | 34 (23–50)                      | 0.2     |
| Number of mpMRI suspicious lesions                | 1 (0–1)            | -                             | 1 (0.3–1.8)                     | 0.1     |
| Maximum lesion diameter on mpMRI                  | 9 (6–13)           | -                             | 9 (6–13)                        |         |
| Gleason score                                      |                    |                               |                                 | 0.3     |
| 3+3=6                                              | 43 (84)            | 17 (100)                      | 26 (76)                         |         |
| 3+4=7                                              | 8 (16)             | 0 (0)                         | 8 (24)                          |         |
| No biopsy taken                                    | 13 (12–14)         | 12 (12–13)                    | 13 (11–15)                      | 0.2     |
| No biopsy with cancer                              | 2 (1–3)            | 1 (1–2)                       | 2.5 (1–4)                       | 0.02    |
| % of biopsies with cancer                          | 4.3 (1–5)          | 1 (1–2.5)                     | 5 (2.5–5.5)                     | 0.05    |
| Maximum cancer burden in a single core %          | 16 (8.5–30)        | 8 (5–15)                      | 21.5 (14.8–30)                  | 0.01    |
| Total cancer core length (mm)                      | 4 (2–8)            | 1.75 (1–2.8)                  | 5 (3–10)                        | 0.03    |
| Maximum cancer burden in a single core length (mm) | 2.5 (1–4)          | 1 (1–1.8)                     | 3 (2–4.8)                       | 0.03    |

Values are presented as number (%) or median (interquartile range).

PSA, prostate-specific antigen; mpMRI, multiparametric magnetic resonance imaging; -, not available.
biopsy and/or MCCL >8 mm), and two in terms of Gleason score (Gleason 4+3). Ten patients (59% of treated patients) underwent RP, three (17%) patients underwent external beam radiotherapy, and four (24%) patients underwent focal therapy.

Of the remaining patients who remained on surveillance, seven progressed from study arm 1 to study arm 2. Five patients progressed because of mpMRI score upgrade, and two patients progressed because of tumor volume progression in the biopsy. Three patients in study arm 2 chose to continue AS despite the violation of one inclusion criteria. They all had PSA levels above 15 ng/mL, with other criteria remaining within the admitted thresholds.

Overall survival, disease-specific survival, and metastasis-free survival were 100%. Among 10 patients who underwent RP, 7 (70%) had T2c disease and 3 (30%) had T3a; none had positive nodes, and one patient had positive margins. Two (20%) had Gleason 3+3=6 disease, seven patients (70%) had Gleason 3+4=7, and one (10%) had Gleason 4+3=7 disease. Among all treated patients, including those undergoing radiation therapy and focal therapy, none had local failure after a median follow-up of 23 months after treatment (IQR, 4–30 months).

Baseline variables potentially predictive for transition to active treatment are shown in Table 4. In the univariate analysis, PI-RADS score, Gleason score, and MCCL in the biopsy seemed relevant predictors of transition to active treatment. In the multivariate analysis, only PI-RADS score and MCCL remained independent predictors.

**DISCUSSION**

To our knowledge, this is the first prospective trial comparing the clinical outcomes of patients with low- and intermediate-risk PCa using a structured protocol embedding mpMRI and MR-targeted biopsies. In brief, we found that AS is a valid option for selected intermediate-risk patients. At 3 years, overall, disease-specific, and metastasis-free survival were all 100% in our study, as expected. Although males with expanded criteria were at greater risk for progression, the window of curability was maintained. PI-RADS score and MCCL were independent predictors for active treatment, underlining the importance of a mpMRI-based pathway.

The primary hypothesis of this trial—a similar transition rate in the two groups—was clearly not met; prolonged follow-up is unlikely to change this as the difference between the two groups was too wide and also considering the available sample size (p=0.0005). Based on the findings of this study, the steering committee amended the initial protocol in 2020: the trial has been modified to a single-cohort study whose objective is to enable the discovery of candidate biomarkers to identify males early who stand to benefit from active therapy and to avoid intervention in those for whom active therapy is not necessary. The novel cohort study embeds tissue and blood biobanks for this
purpose. While all males choosing AS are enrolled in this cohort study, in concordance with the findings of this study, patients are informed about the accrued risk of transition to active treatment according to baseline characteristics (Gleason score and cancer burden).

Comparing our results with others, 21% of 993 males in the Sunnybrook cohort had intermediate-risk features; transition to active treatment was 8% [10] with baseline PSA levels and Gleason score at 1 year associated with failure. This differs from our baseline predictors and active treatment rate. The differences might be due to the different study designs: our study included mpMRI from baseline, whereas in the Sunnybrook series mpMRI was not used routinely. Cooperberg et al. [9] published a series of 540 males with intermediate-risk features managed with AS. After a median of 4 years of follow-up, the number of males presenting with clinical progression was not significantly different between the intermediate-risk (61%) and low-risk (54%) groups (p=0.22). In contrast, patients in our cohort with a PI-RADS score of 1 to 3 and low-volume and low-grade disease had no risk of quitting AS during the study time frame. This strongly suggests that in males with low-risk disease and negative results on mpMRI, the rate of progression is extremely low. In the Prostate Cancer Active Surveillance Study of 115 males with intermediate-risk disease (13% of the cohort) [11] after a median follow-up period of 28 months, 24% of the entire cohort experienced disease reclassification defined by a higher Gleason grade or tumor volume on repeat biopsy. In our study in which we employed similar criteria for transition to radical therapy, the results were analogous: 26% of the males in study arm 2 were reclassified beyond the admitted thresholds of expanded AS criteria.

When assessing those males who underwent RP, our data also indicate the safety of deferred RP as none of our patients had unfavorable pathological features, namely, Gleason ≥4+4, seminal vesicle invasion, or positive lymph nodes. Furthermore, none of them developed biochemical relapse after a median follow-up of 2 years. In the AS series from the Royal Marsden, which included 88 males with intermediate-risk disease, after a median follow-up of 5.7 years, 43 males underwent deferred RP [12]. Of these, 4 (9%) had Gleason score ≥4+4, 6 (14%) had pT3 disease, and 14 (33%) had positive margins. In a Swedish nationwide population-based study, 7,608 males with low-risk disease features had either delayed or immediate prostatectomy [13]. Males undergoing RP more than 2 years after their diagnosis had a higher risk of Gleason upgrading and increased risk for salvage radiotherapy with no significant increase in PCa-specific mortality. These studies once again suggest that upgrading to unfavorable disease in RP specimens might be the result of initial underestimation of disease rather than true disease progression, as the upgrading was based on systematic TRUS biopsy without the use of MRI.

Multiple studies have addressed the importance of mpMRI in AS. Our data suggest that mpMRI plays a key role when predicting failure-free survival. Also, MCCL in the biopsy predicts active treatment better than the Gleason score. This is likely related to imaging, as targeting the center of a lesion leads to greater MCCL than do systematic nontargeted biopsies. Sanguedolce et al. [14] reported similar findings for 135 prospective patients selected for AS by use of the Epstein criteria with mpMRI performed within 3 months of recruitment in AS. At a median follow-up of 31 months, the variables significantly associated with failure-free survival were the index lesion size and overall PI-RADS score. Thurtle et al. [15] published early outcomes from a prospective AS series incorporating image-guided baseline risk assessment and mpMRI-based follow-up in patients with favorable-risk disease. That study confirmed our findings, showing low rates of conversion to active treatment (11.7%) over a median 33 years of follow-up.

There are some limitations to our study. The minimum sample size per group was not met during the recruitment period. This was due to many males being followed with AS but not being eligible for this study and to other males unexpectedly choosing to be followed off-trial. Also, the groups were not balanced, with two-thirds of the study population assigned to the interventional arm. This may have been the result of our more accurate diagnostic pathway, with many males for whom AS could be the preferred option considered ineligible if strict eligibility criteria were systematically applied. It also highlights the changing landscape of PCa in the modern era with stage migration occurring from the use of MRI and targeted biopsies. The small sample size also limits the power of our multivariable analysis including five variables. Finally, the median follow-up was short. Prolonged follow-up is necessary to confirm the oncological outcome of AS across the two groups.

CONCLUSIONS

Expanding the criteria for AS seems to increase the rate of transition to active treatment. Nonetheless, in the short term, the curability window is maintained. PI-RADS score and cancer burden seem the most relevant predictors of disease progression. Confirmatory studies in larger cohorts with longer follow-up are urgently needed to safely broaden the eligibility criteria for AS.
CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS’ CONTRIBUTIONS

Research conception and design: Massimo Valerio, Dominik Berthold, and Patrice Jichlinski. Data acquisition: Arnas Rakauskas, Thomas Tawadros, Maria Natal Gomes, Caroline Codeluppi, Laura Jolliet, Ilaria Lucca, Fernanda Herrera, Jean Bourhis, Rodolfo Burruni, Stefano La Rosa, Jean-Yves Meuwly, Patrice Jichlinski, Dominik Berthold, and Massimo Valerio. Statistical analysis: Arnas Rakauskas, Ilaria Lucca, and Massimo Valerio. Data analysis and interpretation: Arnas Rakauskas, Ilaria Lucca, and Massimo Valerio. Drafting of the manuscript: Arnas Rakauskas. Critical revision of the manuscript: Thomas Tawadros, Maria Natal Gomes, Caroline Codeluppi, Laura Jolliet, Ilaria Lucca, Fernanda Herrera, Jean Bourhis, Rodolfo Burruni, Stefano La Rosa, Jean-Yves Meuwly, Patrice Jichlinski, Dominik Berthold, and Massimo Valerio. Administrative, technical, or material support: Maria Natal Gomes, Caroline Codeluppi, and Laura Jolliet. Supervision: Massimo Valerio and Dominik Berthold. Approval of the final manuscript: Thomas Tawadros, Maria Natal Gomes, Caroline Codeluppi, and Laura Jolliet.

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