Therapy decisions after diagnosis of prostate cancer in men with negative prostate MRI

Florian A. Schmid MD, PhD1 | Laura Lieger MD1 | Karim Saba MD1 | Silvan Sigg MD1 | Fabienne Lehner MD1 | Sharon Waisbrod MD2 | Alexander Müller MD2 | Tullio Sulser MD1 | Daniel Eberli MD, PhD1 | Ashkan Mortezavi MD1,3

1Department of Urology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
2Department of Urology, Spital-Limmattal, Schlieren, Switzerland
3Department of Urology, University Hospital Basel, Basel, Switzerland

Correspondence
Ashkan Mortezavi, MD, Department of Urology, University Hospital Basel, University of Zurich, Spitalstrasse 21, Basel 4056, Switzerland.
Email: ashkan.mortezavi@usb.ch

Funding information
Swiss Cancer League, Grant/Award Number: BIL KLS 4558-08-2018

Abstract
Background: To investigate the clinical implications of magnetic resonance imaging (MRI) negative prostate cancer (PCa) in a cohort of men undergoing transperineal prostate biopsy.

Methods: We included all men without prior diagnosis of PCa undergoing transperineal template saturation ± fusion-guided targeted biopsy of the prostate between November 2014 and March 2018. Before biopsy, all patients underwent MRI and biopsies were performed irrespective of imaging results. Baseline characteristics, imaging, biopsy results, and follow-up information were retrieved from the patient charts. Patients were classified as either MRI negative (Prostate Imaging Reporting and Data System [PIRADS] ≤ 2) or positive (PIRADS ≥ 3). ISUP grade group 1 was defined as clinically nonsignificant (nsPCa) and ≥ 2 as clinically significant PCa (csPCa). Primary outcome was the individual therapeutic decision after diagnosis of PCa stratified according to MRI visibility. Secondary outcomes were the sensitivity and specificity of MRI, and the urooncological outcomes after radical prostatectomy (RP).

Results: From 515 patients undergoing prostate biopsy, 171 (33.2%) patients had a negative and 344 (66.8%) a positive MRI. Pathology review stratified for MRI negative and positive cases revealed nsPCa in 27 (15.8%) and 32 (9.3%) and csPCa in 26 (15.2%) and 194 (56.4%) of the patients, respectively. The rate of active treatment in the MRI negative was lower compared with the MRI positive cohort (12.3% vs. 53.2%; odd ratio [OR] = 0.12; p < 0.001). While men with negative MRI were more likely to undergo active surveillance (AS) than MRI positive patients (18.1% vs. 10.8%; OR = 1.84; p = 0.027), they rarely underwent RP (6.4% vs. 40.7%, OR = 0.10; p < 0.001). Logistic regression revealed that a negative MRI was independently protective for active treatment (OR = 0.32, p = 0.014). The specificity,
sensitivity, negative, and positive predictive value of MRI for detection of csPCa were 49.2%, 88.2%, 56.4%, and 84.8%, respectively. The rate of adverse clinicopathological outcome features (pT3/4, ISUP ≥4, or prostate-specific antigen [PSA]-persistence) following RP was 4.7% for men with MRI negative compared to 17.4% for men with MRI positive PCa (OR = 3.1, p = 0.19).

**Conclusion:** Only few men with MRI negative PCa need active cancer treatment at the time of diagnosis, while the majority opts for AS. Omitting prostate biopsies and performing a follow-up MRI may be a safe alternative to reduce the number of unnecessary interventions.

**KEYWORDS**
biopsy-naïve, imaging, invisible prostate cancer, PIRADS, transperineal biopsy, treatment

---

**1 | INTRODUCTION**

The use of multiparametric magnetic resonance imaging (MRI) in the diagnostic workup of men at risk for prostate cancer (PCa) is advocated by international guidelines. This recommendation counts not only in the repeat-biopsy setting but also for biopsy-naïve patients. Although validating MRI as a triage test for prostate biopsy in men at risk for PCa, recent prospective trials have not been informative on how to optimize the diagnostic algorithm in men with negative MRI. Transperineal template mapping biopsy has been used to determine the negative predictive value (NPV) of MRI. The technique has a clear advantage regarding sensitivity compared to transrectal ultrasound (TRUS) guided random 12-core systematic biopsies. In addition, it avoids the selection bias inherent in using prostatectomy series. According to a Cochrane Review and determined by high coverage biopsy protocols, the NPV of MRI for PCa was reported to be 91% (86%–93%). However, recommendations on the diagnostic workup of men with negative MRI should not only be guided by the number of potentially missed PCa, but also by their clinical significance. Although it has been shown, that MRI visibility is associated with tumor grade and stage, little is known about the clinical consequences of MRI invisible PCa. Considering the yet unclear consequences for the diagnostic workup in men at risk, there is an urgent need to further characterize these tumors. Therefore, the aim of this study was to investigate the clinical implications of MRI invisible PCa diagnosed in a consecutive series of men without prior diagnosis of PCa undergoing transperineal template saturation biopsy compared to men with MRI visible PCa.

**2 | METHODS**

**2.1 | Patient cohort and study design**

This is a retrospective study including all men undergoing MRI of the prostate and subsequent transperineal template saturation prostate biopsy ± fusion-guided targeted biopsy for suspicion of PCa due to elevated prostate-specific antigen (PSA) value or pathological digital rectal examination (DRE) between November 2014 and March 2018 at our tertiary care center. During the entire study period internal clinical guidelines recommended the conduction of prostate biopsies irrespective of the imaging results. In clinical routine, men were scheduled for imaging before prostate biopsy was performed. Patients with a previously established diagnosis of PCa were excluded from the analysis. Our reporting was done in coherence with the recommendations of the START checklist (standard of reporting for MRI targeted biopsy studies). The study was approved by the local ethics committee (KEK-ZH-Nr. 2017-02335).

**2.2 | Clinical characteristics**

The following clinical characteristics were retrieved from the electronic medical as well as radiology and pathology reports: Age, prostate volume, DRE, PSA, previously performed prostate biopsy, date of MRI, radiological classification (highest Prostate Imaging Reporting and Data System [PIRADS] or Likert score per region of interest [ROI] and patient), date of prostate biopsy, performance of systematic and/or targeted biopsies, pathological variables including Gleason score and respective ISUP grade group (GG), maximum cancer core length (MCCL), and subsequent treatment decision for men with PCa. Radical prostatectomy (RP), radiotherapy, high-intensity focused ultrasound (HIFU), and brachytherapy were considered as active treatment options.

**2.3 | Imaging**

Patients were considered for the analysis if they underwent either in-house multiparametric MRI of the prostate or were referred to our institution after having multiparametric MRI performed. All in-house MRI examinations were performed at a field strength of 3 Tesla on...
Siemens Skyra MRI scanners (Siemens Healthineers). Further details regarding magnetic resonance sequences for image acquisition were previously reported by our group (Supporting Information: Table 1).

The images were assessed by board certified radiologists with multiple years of experience in prostate imaging. External images were not routinely reviewed by our in-house radiologists. Evaluation of the imaging was performed in accordance with the technical specifications set forth in the PIRADS version 1 or 2. A suspicious lesion was regarded as PIRADS or Likert score ≥3 per ROI of the prostate. For externally performed MRIs, scores were retrieved from the external report if assessment had been performed according to PIRADS version 1 or 2, and if not available the images were reviewed and scored on a Likert scale 1–5 by in-house radiologists. Patients presenting with multiparametric MRIs with insufficient quality for radiological PIRADS assessment were excluded.

### 2.4 Prostate biopsy

For transperineal prostate biopsies, BiopSEE® software (MedCom) was used to perform real-time TRUS with simultaneous fusion of superimposed MRI images. First, a median of 40 virtual needles were placed for template saturation biopsies. Second, an additional median of 3 targeted biopsies were taken from the regions of interest if the reported PIRADS or Likert score was ≥3. Every single biopsy was numerated and potted separately for histological analysis. Each biopsy core was assessed by specialized uropathologists. An ISUP GG 1 was regarded as clinically nonsignificant PCa (nsPCa), whereas an ISUP GG 2–5 were defined as clinically significant PCa (csPCa). Further, MCCL was reported in mm per positive biopsy.

### 2.5 Therapy and clinical follow-up

The individual therapeutic decisions and details from the clinical follow-up were retrieved from the electronic patient charts (final histology with associated TNM-status, allocated therapy, and PSA follow-up). External urologists or general practitioners were contacted to obtain missing follow-up data if patients were not treated or caretaken at our hospital. Treatment recommendations were proposed by the responsible specialists from the local certified interdisciplinary tumor board. Treatment choice was finally dependent on the counseling urologist and the patients’ preference according to a shared decision making. All cases irrespective of the treatment decision were reviewed prospectively in an interdisciplinary tumor conference and patients considered for surgery were offered counseling by a radio-oncologist. In general, men were eligible for active surveillance (AS) fulfilling following criteria: PSA <10 ng/ml, t<2, ISUP GG 1 (no limitation for number of positive cores or cancer core length), or small volume ISUP GG 2 (<2 mm MCCL). For initiating AS, no confirmatory biopsy was needed. All other ISUP GG triggered active cancer treatment recommendations.

### 2.6 Radical prostatectomy

A transperitoneal robot-assisted laparoscopic approach was used in all patients, as previously described. The decision and extent of nerve sparing was decided on an individual level according to oncological feasibility. The indication for lymph node dissection was based on the surgeons’ and/or patients’ preference according to a shared decision making and not based on any risk calculator. Routinely, an extended lymph node dissection was performed as described by Feicke et al. Adverse clinicopathological outcome features in the prostatectomy specimen were defined as patients harboring pT3/4, ISUP GG 4/5, and PSA-persistence.

### 2.7 Statistical analysis

Statistical analysis was performed using the software R for statistical computing (version 4.0.2). Descriptive statistics were reported as absolute numbers, proportions and means with standard deviations. Results were presented stratified according to findings on MRI: Patients were classified as MRI positive if the reported PIRADS or Likert score was ≥3. Men with PIRADS or Likert score ≤2 were considered as MRI negative. Binary, categorical, and continuous variables were compared using Pearson’s χ², Mann–Whitney U, and Welch t-test, respectively. A multivariable regression analysis was fitted to predict the need for active therapy according to negative MRI status adjusted for baseline characteristics age <65 years, higher prostate volume, inconspicuous DRE, PSA <10 ng/ml, PSA density <0.1 ng/ml/² prior biopsies, and ISUP <GG 2–5. A further multivariable regression analysis was employed to predict csPCa by negative MRI status adjusted for the above-mentioned baseline characteristics. A descriptive subgroup analysis was performed to further analyze the MRI negative cohort with PCa and csPCa stratified by AS versus active treatment. An additional univariable regression analysis was fitted to investigate the prediction of csPCa and active treatment through PSA density with designated cutoff values 0.25 and 0.1 ng/ml. At last, a descriptive analysis of all patients with PIRADS 3 as highest MRI lesion was conducted. p ≤ 0.05 were considered statistically significant (two-sided).

### 3 RESULTS

Throughout the observation period 515 consecutive patients were included in the analysis. Clinical characteristics (age, prostate volume, and PSA values) were evenly distributed among the groups of MRI negative and MRI positive patients, except for pathological DRE and PSA-density (Table 1). Among all biopsied men, 236 (45.8%) had a negative biopsy result (benign histology), 59 (11.5%) had nsPCa (ISUP GG 1), and 220 (42.7%) had csPCa (ISUP GG 2–5).

More than three-quarters of all MRIs were performed in-house (78.1%, n = 402), whereas 21.9% (n = 113) were conducted and evaluated by external radiologists. A total of 171 (33.2%) patients had
no suspicious MRI lesion (MRI negative), whereas 344 (66.8%) patients had at least one lesion classified as PIRADS or Likert ≥3 (MRI positive). Pathology review stratified for MRI negative and MRI positive cases revealed nsPCa in 27 (15.8%) and 32 (9.3%), csPCa in 26 (15.2%) and 194 (56.4%) of the cases, respectively (Table 2).

The specificity and sensitivity of the MRI assessed by transperineal prostate biopsy for the detection of csPCa were calculated at 49.2% and 88.2%, whereas the NPV and positive predictive value were 56.4% and 84.8%, respectively. The chance of being diagnosed with nsPCa was higher after a negative MRI result (15.8% vs. 9.3%, p = 0.070; OR = 0.16; 95% CI: 0.08–0.32). The MRI negative cohort was smaller according to MCCL of systematic prostate biopsies (1.14 vs. 3.56 mm; 95% CI: −3.05 to −1.79; p < 0.001) (Table 2).

According to the results from the multivariable regression analysis, a negative MRI was protective for the presence of csPCa as an independent and statistically significant predictor after adjusting for all relevant baseline characteristics (OR = 0.21; 95% CI: 0.10–0.43; p < 0.001). Therefore, men with a negative MRI had a 79% lower chance of having csPCa compared to MRI positive patients (Table 3a).

The rate of active cancer treatment in the MRI negative cohort was lower compared with the MRI positive group (n = 21 vs. n = 183; 12.3% vs. 53.2%; OR = 0.12; 95% CI: 0.07–0.20; p < 0.001). AS was chosen in 18.1% (n = 31) in the MRI negative versus 10.8% (n = 37) in the MRI positive cohort. Therapeutic pathways in the MRI negative versus MRI positive cohorts were chosen as follows: RP (6.4% vs. 40.7%), radiotherapy (2.3% vs. 4.7%), HIFU (1.2% vs. 5.8%), or brachytherapy (2.3% vs 2.0%). While men with negative MRI were more likely to undergo AS compared to patients with positive MRI (18.1% vs. 10.8%; OR = 1.84; 95% CI: 1.10–3.08; p = 0.027), they rarely underwent RP (OR = 0.10; 95% CI: 0.05–0.19; p < 0.001).

The stratification based on our definition of clinical relevance revealed that 81% of the men with csPCa and no men with nsPCa received active cancer treatment in the MRI negative cohort. Further details regarding treatment decisions and their rate in respect to the total MRI negative and positive cohort are presented in Table 2.

In the multivariable regression analysis, a negative MRI was protective for the need of any form of active cancer treatment (RP, radiotherapy, HIFU, or brachytherapy) as an independent and statistically significant predictor even after adjusting for all relevant baseline characteristics as well as ISUP <GG 2 (OR = 0.32; 95% CI: 0.13–0.79; p = 0.014). According to this, men with a negative MRI...
TABLE 3a Results from multivariable regression analysis of negative MRI for the prediction of csPCa adjusted for baseline characteristics (age, prostate volume, DRE, PSA, PSA density, and prior biopsy) and ISUP GG (1 vs. 2)

| csPCa                                      | OR   | 95% confidence interval | p Value |
|--------------------------------------------|------|-------------------------|---------|
| MRI negative                               | 0.21 | 0.10 (–0.43)            | <0.001*** |
| Age < 65                                   | 0.62 | 0.31 (–1.25)            | 0.18    |
| Higher prostate volume                     | 0.98 | 0.97 (–1.00)            | 0.033*  |
| DRE inconspicuous                          | 0.35 | 0.16 (–0.80)            | 0.012*  |
| PSA < 10 ng/ml                             | 0.47 | 0.18 (–1.20)            | 0.11    |
| PSA density < 0.1 ng/ml^2                  | 0.41 | 0.18 (–0.93)            | 0.032*  |
| Prior Bx                                   | 0.90 | 0.42 (–1.94)            | 0.79    |

Note: All dichotomous, except one continuous variable (prostate volume). *p<0.05, **p<0.01, ***p<0.001.
Abbreviations: Bx, biopsy; csPCa, clinically significant prostate cancer (ISUP GG 2–5); DRE, digital rectal examination; GG, grade group; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

TABLE 3b Results from the multivariable regression analysis of negative MRI for the prediction of an active therapy decision adjusted for baseline characteristics (age, prostate volume, DRE, PSA, PSA density, and prior biopsy) and ISUP GG (1 vs. 2–5)

| Active therapy | OR   | 95% confidence interval | p Value |
|----------------|------|-------------------------|---------|
| MRI negative   | 0.32 | 0.13 (–0.79)            | 0.014*  |
| Age < 65       | 1.13 | 0.49 (–2.62)            | 0.78    |
| Higher prostate volume | 1.01 | 0.99 (–1.03)         | 0.41    |
| DRE inconspicuous | 0.38 | 0.15 (–0.96)            | 0.04*   |
| PSA < 10 ng/ml | 1.59 | 0.61 (–4.16)            | 0.35    |
| PSA density < 0.1 ng/ml^2                  | 0.65 | 0.21 (–2.00)            | 0.45    |
| Prior Bx      | 1.06 | 0.42 (–2.70)            | 0.89    |
| ISUP < GG 2–5 | 0.02 | 0.01 (–0.05)            | <0.001*** |

Note: All dichotomous, except one continuous variable (prostate volume). *p<0.05, **p<0.01, ***p<0.001.
Abbreviations: Bx, biopsy; csPCa, clinically significant prostate cancer (ISUP GG 2–5); DRE, digital rectal examination; GG, grade group; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

had an 68% lower chance of receiving active cancer treatment compared to MRI positive patients (Table 3b).

If patients with a negative MRI would not have been biopsied, 45.8% (27 out of 59) of nsPCa diagnosis could have been avoided and 11.8% (26 out of 220) of csPCa would not have been detected. The number needed to biopsy to detect one additional csPCa in MRI negative men was 7. Contingency tables regarding the presence of no PCa versus any PCa and nsPCa versus csPCa in patients undergoing saturation (MRI negative) versus saturation + targeted (MRI positive) prostate biopsies according to START criteria are shown as Supporting Information: - Table 2a-2b.

A subgroup analysis in the cohort of MRI negative men with any PCa revealed that patients with active treatment tended to have a higher mean PSA value (13.4 [17.1] vs. 7.17 [5.7] ng/ml^2), a higher mean PSA density (0.29 [0.41] vs. 0.14 [0.09] ng/ml^2), and higher ISUP GG than those undergoing AS (Supporting Information: Table 3a).

To assess the drivers of active treatment versus AS in MRI negative men with csPCa on biopsy, an additional subgroup analysis was performed (Supporting Information: Table 3b). Out of 26 men with MRI negative csPCa, 19 (73.1%) underwent active treatment and 7 (26.9%) patients opted for AS. The mean PSA density was 0.32 [0.42] for active therapy and 0.15 [0.09] ng/ml^2 in AS. The according univariable regression analysis demonstrated that PSA density with a cutoff value of 0.25 and 0.1 ng/ml^2 was neither a statistically significant predictor of csPCa (OR = 0.43; 95% CI: 0.12–1.52; p = 0.19 and OR = 0.34; 95% CI: 0.11–1.08; p = 0.07, respectively), nor of active treatment in the subgroup of MRI negative men (OR = 0.39; 95% CI: 0.11–1.37; p = 0.14 and OR = 0.61; 95% CI: 0.19–1.92; p = 0.4, respectively). Please find results displayed as Supporting Information: Table 4a-b. Finally, a descriptive subgroup analysis was performed to display the cohort of men with PI-RADS 3 result on MRI regarding baseline characteristics, biopsy results and therapeutic pathways (Supporting Information: Table 5). In this cohort, any PC and csPCa was detected in 43 (42.6%) and in 29 (28.7%), respectively. The majority of men with a PI-RADS 3 as highest MRI lesion and subsequent PCa underwent active cancer treatment (n = 29/43, 67.4%).

A comparison of the histological results and the PSA-values during uro-oncological follow-up in the two cohorts of patients after RP (n = 11 vs. n = 140 in the MRI negative vs. MRI positive cohort, respectively) is shown in Table 4. Differences were found in the distribution of ISUP GG, the percentage of pT3 and pN1 status, as well as the rate of positive surgical margins between the groups of MRI negative versus MRI positive men. PSA-values 6 weeks after RP were comparable between the two groups: Overall 97.9% of patients had an undetectable PSA at the first oncological follow-up, independent of the initial MRI status. Based on the total cohort of men with negative and positive MRI, the rate of adverse clinicopathological and uro-oncological outcome features (pT3/pN1, ISUP GG 4/5, or PSA-persistence) following RP was 4.7% versus 17.4% (OR = 3.1; 95% CI: 0.62–15.1; p = 0.19), respectively. The number needed to biopsy in the MRI negative cohort to detect one additional man with adverse clinicopathological and uro-oncological outcome features after RP was 22. Comparison of baseline characteristics in the RP cohort are shown in Supporting Information: Table 6.

4 | DISCUSSION

Since the introduction of MRI in the diagnostic pathway of PCa, the indication for performing systematic biopsies in men with negative MRI (PI-RADS score 1 or 2) has been controversially discussed in
clinical practice as well as the scientific community.\textsuperscript{15,16} Although the rate of unnecessary biopsies with benign histology is up to 94% in this cohort,\textsuperscript{17} many clinicians fear missing csPCa not detected on MRI (either “true-negative” or false-negative MRI as missed in radiological assessment) with subsequent therapeutic implications for these patients. To mitigate this issue, risk calculator driven decision making incorporating MRI results or PSA density have been proposed.\textsuperscript{18,19} In the present trial we did not focus on the prediction of cancer in men with negative MRI, but rather aimed to assess the clinical relevance of tumors in MRI-negative patients. If it turns out, that these tumors are rarely in need for treatment at the time of imaging, then further risk stratification with prostate (saturation) biopsy after negative MRI may become unnecessary. Indeed, we observed that out of 171 men with negative MRI undergoing template saturation biopsies, only 4 out of 114 patients (3.6%) demonstrated intermediate (19.3%) and could remain on AS. Only 4 out of 114 patients (3.6%) demonstrated intermediate-risk disease and subsequently needed any form of active cancer therapy.\textsuperscript{15} Meanwhile, the independent risk factors age, PSA, prostate volume, and T-stage ≥ 2 were no predictors of active cancer therapy.\textsuperscript{15} Further, a series of RPs after negative MRI published by Branger et al.\textsuperscript{21} demonstrated intermediate-risk disease and subsequently needed any form of active cancer therapy.\textsuperscript{15} Therefore, performance of prostate biopsy has been proposed only if high-risk features such as high PSA values, positive DRE, younger age, positive family history, and/or suspicion of cT2c on MRI are present.\textsuperscript{24} However, no clear cut-offs for these parameters have been defined, whereas our multivariable regression analysis showed, that a negative MRI significantly reduces the risk for the need of an active treatment independent of these risk-factors. According to An et al.,\textsuperscript{15} most men after negative MRI and subsequent systematic 12-core biopsy had benign history (77.2%) or low-risk disease (19.3%) and could remain on AS. Only 4 out of 114 patients (3.6%) demonstrated intermediate-risk disease and subsequently needed any form of active cancer therapy.\textsuperscript{15} The Kaplan–Meyer analysis of these 659 biopsy naïve and MRI negative men have shown 2-year diagnosis-free survival probabilities of 94% and 95% for any grade PCa and csPCa, respectively.\textsuperscript{25} The Kaplan–Meyer analysis of these 659 biopsy naïve and MRI negative men have shown 2-year diagnosis-free survival probabilities of 94% and 95% for any grade PCa and csPCa, respectively.\textsuperscript{25} The Kaplan–Meyer analysis of these 659 biopsy naïve and MRI negative men have shown 2-year diagnosis-free survival probabilities of 94% and 95% for any grade PCa and csPCa, respectively.\textsuperscript{25} Unfortunately, no information regarding treatment modality was presented. In the PROMIS trial, Ahmed et al.\textsuperscript{8} performed transperineal template mapping biopsies in 576 men after MRI, whereas NPV for csPCa was calculated at 76% (69–82%). A plausible explanation for the lower NPV in our cohort (56.4%) may be the non-standardized review of prostate MRIs outside of a trial setting (with arguably higher rate of false-negative radiological evaluations) and the potentially higher number of cores in the systematic biopsies (exact median core number not provided in the PROMIS trial). However, and in contrast to the PROMIS trial

| T-cell status (%) | MRI negative | MRI positive |
|------------------|--------------|--------------|
| pT2a-c           | 8 (4.7)      | 86 (25.0)    |
| pT3a             | 3 (1.8)      | 34 (9.9)     |
| pT3b             | 0 (0.0)      | 10 (2.9)     |

| N-status (%)     | MRI negative | MRI positive |
|------------------|--------------|--------------|
| pN1              | 0 (0.0)      | 12 (3.5)     |

| Positive surgical margin (%) | MRI negative | MRI positive |
|------------------------------|--------------|--------------|
| PSA persistence > 0.1 ng/ml  | 2 (1.2)      | 9 (2.6)      |

Abbreviations: GG, grade group; LN, lymph nodes; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy.
facilitating ideal radiological assessment with centralized radiological training and reviews between centers, our data reflect an unselected patient cohort with transperineal saturation biopsies after MRI. The diagnostic precision is dependent on the biopsy technique (transrectal mapping vs. transperineal saturation biopsies) as well as the number of samples taken (median core number). As an example, the study by Thompson et al.\textsuperscript{5} shows that in 22.9% of patients with a negative MRI and subsequent transperineal template biopsy, 7.4% of men harbored low- to intermediate-risk PCAs (ISUP GG 1–2). However, the protocol with a median of 30 cores as reference was less rigorous than our study protocol with a median core amount of 40 biopsies.\textsuperscript{5} For comparison, our results showed that out of 32.2% of patients with a negative MRI, only in 25.7% a low- to intermediate risk PCa (ISUP GG 1–2) was found. Finally, our subgroup analysis of men with a PIRADS 3 as highest MRI lesion revealed that a significant number harbor csPCa and that all of them undergo active treatment. This finding underlines the distinct dissimilarity of PIRADS 1–2 versus 3 lesions and the different clinical relevance of such a finding.

4.1 Limitations

There are some limitations to this study. First, it is a retrospective study and no protocols or guidelines were implemented for treatment recommendations in men diagnosed with PCa. Decision making was dependent on counseling of the treating urologist and patients’ choice. Policies may differ in other geographical regions or hospitals. However, the eligibility criteria for AS was similar to published reports of other large cohorts and ongoing trials, although without core number restrictions due to the saturation biopsy approach. Furthermore, a missed diagnosis of an actual MRI visible tumor by the radiologist cannot be ruled out, since review took place in a clinical routine setting without central reviews. At the same time, a low rate of missed diagnoses is part of clinical practice, and the present data will give a more realistic statement on the detection rate and clinical features of MRI negative PCa in daily routine. Finally, no long-term follow-up was available regarding the frequency of AS dropout (no follow-up data neither on confirmatory biopsies, nor potential cancer progression) and biochemical recurrence rates in patients receiving active tumor treatment.

The strength of the study is that all men underwent template saturation biopsies regardless of the MRI outcome, avoiding a selection bias in the MRI negative cohort. It can be assumed that template saturation biopsies with a median of 40 cores per patient have a high sensitivity to detect most tumors in a cohort of men without a lesion on MRI. And finally, except for patient with an MRI-negative PCa, follow-up on treatment decisions were available.

5 CONCLUSION

MRI negative PCa diagnosed by systematic template saturation biopsies in an unselected cohort of men can be classified as clinically insignificant in most cases. In our experience, only few men with negative MRI and PCa needed active cancer treatment at the time of diagnosis, while most underwent AS. Omitting prostate biopsies and performing a follow-up MRI may be a safe alternative to reduce the number of unnecessary interventions.

ACKNOWLEDGMENT

This study was supported from the Swiss Cancer League (A. M. receives funding, BIL KLS 4558-08-2018). Open access funding provided by Universitat Zurich.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Florian A. Schmid http://orcid.org/0000-0002-0862-5027

REFERENCES

1. Mottet N, van den Bergh R, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2021;79(2):243-262.
2. Bjurlin MA, Carroll PR, Eggener S, et al. Update of the standard operating procedure on the use of multiparametric magnetic resonance imaging for the diagnosis, staging and management of prostate cancer. J Urol. 2020;203(4):706-712.
3. NICE Guidance. Prostate cancer: diagnosis and management 2019. BJU Int. 2019;124(1):9-26.
4. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767-1777.
5. Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol. 2016;195(5):1428-1435.
6. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815-822.
7. Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019;4:CD012663.
8. Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol. 2015;67(3):569-576.
9. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. Eur Urol. 2013;64(4):544-552.
10. Mortezavi A, Mährendorfer O, Donati OF, et al. Diagnostic accuracy of multiparametric magnetic resonance imaging and fusion guided targeted biopsy evaluated by transperineal template saturation biopsy for the detection and characterization of prostate cancer. J Urol. 2018;200(2):309-318.
11. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging—reporting and data system: 2015, version 2. Eur Urol. 2016;69(1):16-40.
12. Barentsz JO, Richenber J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22(4):746-757.
13. Feicke A, Baumgartner M, Talimi S, et al. Robotic-assisted laparoscopic extended pelvic lymph node dissection for prostate cancer: surgical technique and experience with the first 99 cases. *Eur Urol*. 2009;55(4):876-883.

14. R Core Team. *R: a Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2017. https://www.R-project.org/

15. An JY, Sidana A, Holzman SA, et al. Ruling out clinically significant prostate cancer with negative multi-parametric MRI. *Int Urol Nephrol*. 2018;50(1):7-12.

16. Branger N, Maubon T, Traumann M, et al. Is negative multi-parametric magnetic resonance imaging really able to exclude significant prostate cancer? The real-life experience. *BJU Int*. 2017;119(3):449-455.

17. Barkovich EJ, Shankar PR, Westphalen AC. A systematic review of the existing prostate imaging reporting and data system version 2 (PI-RADSv2) literature and subset meta-analysis of PI-RADSv2 categories stratified by Gleason scores. *AJR Am J Roentgenol*. 2019;212(4):847-854.

18. Saba K, Wettstein MS, Lieger L, et al. External validation and comparison of prostate cancer risk calculators incorporating multiparametric magnetic resonance imaging for prediction of clinically significant prostate cancer. *J Urol*. 2020;203(4):719-726.

19. Mortezavi A, Eklund M, Bergman M, Kjosavik SR, Discacciati A, Nordström T. Association between PSA density and prostate cancer in men without significant MRI lesions. *BJU Int*. 2020;125(6):763-764.

20. Wallström J, Geterud K, Kohestani K, et al. Prostate cancer screening with magnetic resonance imaging: results from the second round of the göteborg prostate cancer screening 2 trial. *Eur Urol Oncol*. 2022;5(1):54-60.

21. Stabile A, Giganti F, Emberton M, Moore CM. MRI in prostate cancer diagnosis: do we need to add standard sampling? A review of the last 5 years. *Prostate Cancer Prostatic Dis*. 2018;21(4):473-487.

22. Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. *BJU Int*. 2016;118(4):515-520.

23. Yerram NK, Volkin D, Turkbey B, et al. Low suspicion lesions on multiparametric magnetic resonance imaging predict for the absence of high-risk prostate cancer. *BJU Int*. 2012;110(11 pt B):E783-E788.

24. Schoots IG, Padhani AR. Delivering clinical impacts of the MRI diagnostic pathway in prostate cancer diagnosis. *Abdom Radiol*. 2020;45(12):4012-4022.

25. Panebianco V, Barchetti G, Simone G, et al. Negative multiparametric magnetic resonance imaging for prostate cancer: what’s next? *Eur Urol*. 2018;74(1):48-54.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Schmid FA, Lieger L, Saba K, et al. Therapy decisions after diagnosis of prostate cancer in men with negative prostate MRI. *The Prostate*. 2023;83:56-63. doi:10.1002/pros.24435