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Prostate Cancer

Prostate Biopsies Can Be Omitted in Most Patients with a Positive Stockholm3 Test and Negative Prostate Magnetic Resonance Imaging

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Abstract

Background: Magnetic resonance imaging (MRI) combined with the Stockholm3 test can be used to inform biopsy decision-making in patients with a suspicion of prostate cancer.
Objective: To determine the consequence of omitting biopsies in men with a positive Stockholm3 test and a negative MRI.
Design, setting, and participants: In a real-life setting, 438 men with a positive Stockholm3 test and a negative MRI underwent systematic biopsies from 2017 to 2020.
Outcome measurements and statistical analysis: The Stockholm3 test result is a percentage risk score with or without a prostate volume cutoff. The main outcomes were the number of clinically significant (Gleason grade group [GG] ≥2) and nonsignificant (GG 1) prostate cancers.
Results and limitations: Median prostate-specific antigen was 4.5 ng/ml (interquartile range 2.8–6.4 ng/ml) and the median age was 69 yr. Systematic biopsies detected grade group (GG) ≥2 disease in 48 men (11%, 95% confidence interval [CI] 8.4–14.2%) and GG 1 disease in 94 men (21.5%, 95% CI 17.9–25.6%). Of 256 patients without a volume cutoff in the test report, GG ≥2 was detected in 37 men (14.5%, 95% CI 10.7–19.3%). Omitting biopsies in patients with a volume cutoff would miss 11 GG ≥2 cases (6%, 95% CI 3.4–10.5%), reduce the number of GG 1 cases detected by 37 (39.4%, 95% CI 30.1–49.5%), and avoid a total of 182 biopsies (41.6%, 95% CI 37.0–46.2%). Limitations include the lack of follow-up data.
Conclusions: Systematic biopsies can be omitted in patients with a positive Stockholm3 test and a negative MRI when there is a volume cutoff in the test report. With no volume cutoff, biopsies can be considered with shared decision-making.

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Patient summary: When investigated on suspicion of prostate cancer with a positive Stockholm3 test and a negative MRI (magnetic resonance imaging), prostate biopsies are only necessary for a subgroup of patients. This can spare some men from undergoing biopsies and reduce the detection of clinically insignificant cancers.

1. Introduction

International guidelines recommend the addition of prebiopsy multiparametric magnetic resonance imaging (MRI) to prostate-specific antigen (PSA) and digital rectal examination (DRE) in prostate cancer (PCa) diagnostics [1]. According to the International Society of Urological Pathology (ISUP), MRI has excellent sensitivity for detection of clinically significant PCa (csPCa = grade group [GG] ≥2) [2,3], and studies report that it has a high negative predictive value in excluding csPCa [4,5].

The benefit of performing systematic biopsies in patients with a negative MRI differs between the biopsy-naïve and repeat biopsy settings, with fewer cancers being missed in the latter [6–8]. Depending on the setting, the proportion of missed cancers reported appears to be wide, between 7% and 55% [9–11]. However, unnecessary biopsies may cause harm and are associated with patient burden, a non-negligible risk of infection with transrectal biopsies, potential overdiagnosis, and possible overtreatment.

Better strategies for patient selection are called for. For patients with PSA >3 ng/ml, the addition of PSA density (PSA-D) for risk stratification increases the predictive value of MRI [12–14]. Use of PSA-D categories and MRI may help in selecting patients for biopsies [15] and is recommended by the European Association of Urology (EAU) guidelines [1].

Different risk calculators have been developed to predict subsequent biopsy results. One of these is the Stockholm3 test, which includes clinical data (previous biopsy, prostate volume, and DRE) and reduces overdiagnosis and the number of biopsies performed while maintaining sensitivity for the detection of GG ≥2 cancers [16]. The Stockholm3 test has also been used in combination with MRI to inform biopsy decision-making [17].

The aim of this study was to analyze the clinical consequences of omitting biopsies in patients with a positive Stockholm3 test and a negative MRI.

2. Patients and methods

2.1. Study setting

The study was performed in a real-life clinical setting in the Stavanger region, Norway, covering a population of 372 000 inhabitants with approximately 330 general practitioners (GPs) in 94 offices [18]. Stavanger University Hospital has routinely used prebiopsy MRI in PCa diagnostics since 2013. From September 2017, all GPs in the region received a recommendation to change their blood testing practice from PSA to the Stockholm3 test in men without known PCa. Our study includes men without a previous PCa diagnosis who had a positive Stockholm3 test and underwent MRI of the prostate from September 2017 to December 2020. The positive Stockholm3 test was registered no more than 6 mo before the MRI. The MRI scans included had a Prostate Imaging-Reporting and Data System (PI-RADS) score of 1–2 and were considered negative, and all men underwent biopsies within 6 mo of the MRI.

The Regional Committee for Medical and Health Research Ethics approved the study (REK 2017/71 REK-vest). The study is registered on ClinicalTrials.gov as NCT03381105.

2.2. Study population

During the study period, 3687 prostate MRIs were performed, of which 1277 were positive and were excluded from the analysis. MRIs were also excluded if the investigation was incomplete or if consent was lacking. MRIs performed in men with known PCa or for other indications were also excluded.

Of the 1350 negative MRI scans, cases without a Stockholm3 test or with a negative result, and cases lacking biopsy within 6 mo after their MRI were excluded (Fig. 1). In total, 438 unique patients with a positive Stockholm3 test, a negative MRI, and known biopsy results were included.

Medical records for the 132 men who did not undergo biopsies within 6 mo of their MRI revealed that the urologist did not recommend biopsy because the perceived risk of csPCa was low. The recommendation for these men was to monitor their PSA twice yearly and have a new Stockholm3 test in 1–2 yr.

2.3. The Stockholm3 test

GPs ordered the Stockholm3 test applying similar indication criteria as for PSA for men being investigated on suspicion of PCa. The Stockholm3 test was not performed during follow-up of men with known PCa. The result of a Stockholm3 test is a risk score given as a percentage. Further PCa diagnostic tests were at that time recommended for patients with a Stockholm3 test result ≥11%. For patients with a positive test, recommendations are divided into two categories. For some patients, MRI and biopsy are recommended regardless of prostate volume (ie, without a volume cutoff). For the other group, MRI and biopsies are indicated with a prostate volume lower than a certain cutoff calculated and given in the report.

When the Stockholm3 test was introduced in the study region, it was only validated for men aged 50–69 yr. The test was nevertheless recommended regardless of age in the Stavanger region. For this reason, the analyses are stratified by age <70 yr versus ≥70 yr. This also corresponds to ages above and below the median age at diagnosis for the study cohort and represents the distinction between older and younger patients often applied in routine clinical practice.

2.4. MRI protocol and interpretation

Before biopsies, biparametric MRI was performed using a 1.5-T or 3.0-T magnet with a phased-array coil. Imaging was three-dimensional T2-weighted imaging of the pelvis with coronal T1 series of the lumbar

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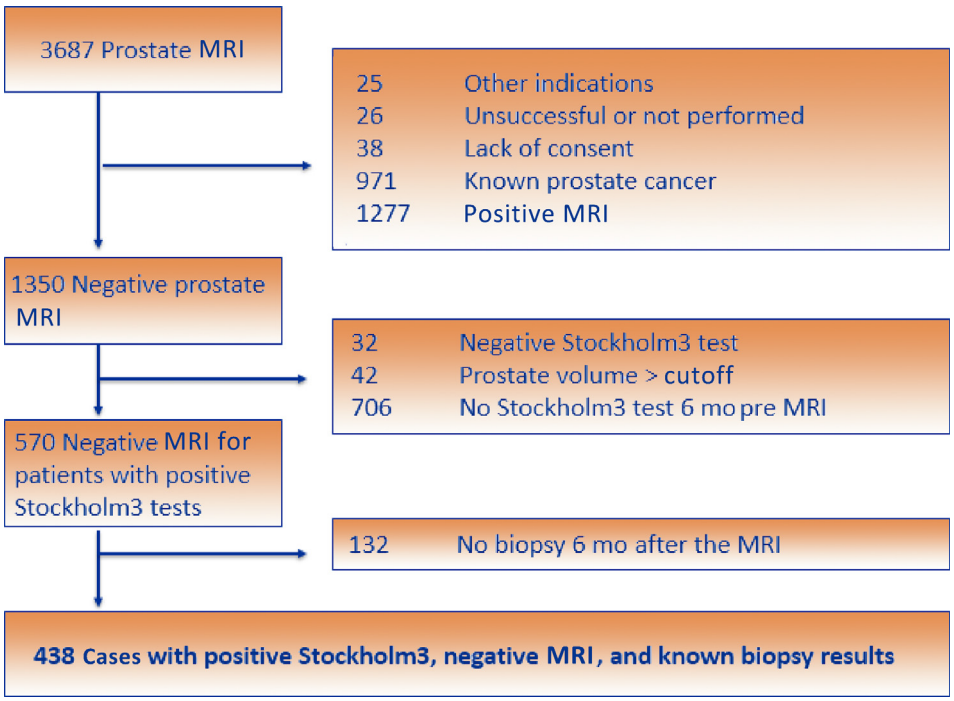

Fig. 1 – Flow chart for the study population. MRI = magnetic resonance imaging.

spine and pelvis, and diffusion-weighted imaging (DWI) as the functional technique. Dynamic contrast-enhanced series (multiparametric MRI) were performed only in 24 men with a hip prosthesis.

Most images were evaluated by a senior dedicated uroradiologist without a second reading. When images were read by a less experienced radiologist, there was an additional second reading. Images were assessed using PI-RADS version 2 from 2018 and version 2.1 from January 2020. The examination was considered negative with an assigned PI-RADS score of 1–2.

2.5. *Biopsies and significant cancer assessment*

All patients underwent standard 12-core transrectal prostate biopsies with prophylactic antibiotics. The biopsy specimens were fixed in formaldehyde. All biopsies were reviewed by experienced pathologists at Stavanger University Hospital and graded according to the ISUP 2014 modification.

csPCa was defined as GG ≥2 and nonsignificant PCa as GG 1. All positive prostate biopsies (GG ≥1) were discussed in multidisciplinary meetings using pathological correlation and feedback and with individual recommendations on further follow-up and treatment.

Before data collection, 5% was defined as an acceptable rate of csPca cases missed. A rate of 5–10% was dependent on the ISUP grade of cancers missed, and >10% was considered unacceptable for clinicians.

2.6. *Statistical analysis*

Descriptive statistics are presented as the median and interquartile range (IQR) for continuous variables and as frequency and percentage for categorical variables. Categorical outcomes are presented with 95% Wilson confidence intervals (CI) estimated using the online calculator at OpenEpi.com. Ordered categorical outcomes were compared between groups using the Mann-Whitney *U* test, with exact two-sided *p* values presented. A *p* value <0.05 was considered statistically significant.

Statistical analysis was performed using SPSS version 29.0.0.0 (IBM Corp., Armonk, NY, USA).

3. Results

Of the 438 patients included, 250 were aged <70 yr and 188 were aged ≥70 yr (Table 1). The median Stockholm3 risk score was 21% (IQR 16–30%) and median PSA was 4.5 ng/ml (IQR 2.8–6.4 ng/ml). Among these participants, 421 (96%, 95% CI 93.9–97.6%) were biopsy-naïve. None of the 17 men (3.9%, 95% CI 2.4–6.1%) with a previous biopsy was diagnosed with PCa.

Systematic biopsies detected PCa in 142 men (32.4%, 95% CI 28.2–36.9%), and this was GG ≥2 in 48 (11%, 95% CI 8.4–14.2%). Of men with no volume cutoff in their Stockholm3 test report, 37 (14.5%, 95% CI 10.7–19.3%) had GG ≥2 disease. Among the men with a test report that included a volume cutoff, GG ≥2 disease was found in 11 (6%, 95% CI 3.4–10.5%). No men had metastatic disease at the time of diagnosis.

The outcomes for different Stockholm3 risk scores are given in Table 2, including whether there was a volume cutoff in the report or not. Whether or not the Stockholm3 report included a volume cutoff correlated with biopsy results. Reports without a volume cutoff had a higher probability of detecting cancer in the biopsies ($p = 0.009$). None of the patients with a Stockholm3 risk score ≥30% had a volume cutoff in their report.

The 22 men (5.0%, 95% CI 3.34–7.5%) who underwent radical treatment with either radical prostatectomy or external beam radiotherapy had GG ≥2 disease (Fig. 2). To treat the 16 patients (6.3%, 95% CI 3.9–9.9%) without a volume cutoff in their Stockholm3 test report, 256 biopsies needed to be performed. The 26 patients (54.2 %, 95% CI

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Table 1 – Patient characteristics and results stratified by age and, with or without volume cutoff

	Age <70 yr		Age ≥70 yr	
	N	Result	*N*	Result
Stockholm3 with VCO	136		46	
Median age, yr (IQR)		62 (10)		72 (4)
Median SRS, % (IQR)		16 (5)		15 (3)
Median PSA, ng/ml (IQR)		3.1 (2.2)		2.8 (1.6)
Bx result, % (95% CI)				
Benign	97	71.3 (63.2–78.3)	37	80.4 (66.8–89.4)
GG 1	33	24.3 (17.8–32.1)	4	8.7 (3.4–20.3)
GG 2	5	3.7 (1.6–8.3)	4	8.7 (3.4–20.3)
GG 3	1	0.7 (0.13–4.0)		
GG ≥4			1	2.2 (0.4–11.3)
Stockholm3 without VCO	114		142	
Median age, yr (IQR)		65 (8)		73 (4)
Median SRS, % (IQR)		27 (11)		28 (17)
Median PSA, ng/ml (IQR)		5.9 (3.2)		5.4 (4.1)
Bx result, % (95% CI)				
Benign	80	70.2 (61.2–77.8)	82	57.7 (49.5–65.6)
GG 1	22	19.3 (13.1–27.5)	35	24.6 (18.3–32.3)
GG 2	9	7.9 (4.2–14.3)	16	11.3 (7.1–17.5)
GG 3	2	1.8 (0.5–6.2)	7	5.0 (2.4–9.8)
GG ≥4	1	0.9 (0.2–4.8)	2	1.4 (0.4–5.0)

Bx = biopsy; CI = confidence interval; GG = International Society of Urological Pathology grade group; IQR = interquartile range; PSA = prostate-specific antigen; SRS = Stockholm3 risk score; VCO = volume cutoff.

Table 2 – Distribution of biopsy results stratified by Stockholm3 risk scores with or without a volume cutoff

	Stockholm3 with volume cutoff				Stockholm3 without volume cutoff					
	RS 11–14%		RS 15–29%		RS 11–14%		RS 15–29%		RS ≥30%	
Patients (*N*)	72		110		6		134		116	
Bx result	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	n	% (95% CI)	*n*	% (95% CI)
Benign	59	81.9 (71.5–89.1)	75	68.2 (59.0–76.2)	5	83.3 (43.7–97.0)	91	67.9 (59.6–75.2)	66	56.9 (47.8-65.6)
GG 1	7	9.7 (4.8–18.7)	30	27.3 (19.8–36.3)			23	17.2 (11.7–24.4)	34	29.3 (21.8–38.2)
GG 2	5	6.9 (3.0–15.3)	4	3.6 (1.4–9.0)	1	16.7 (3.0–56.4)	15	11.2 (6.9–17.7)	9	7.8 (4.1–14.1)
GG 3			1	0.9 (0.2–5.0)			3	2.2 (0.8–6.4)	6	5.2 (2.4–10.8)
GG ≥4	1	1.4 (0.2–7.5)					2	1.5 (0.4–5.3)	1	0.9 (0.2–4.7)

Bx = biopsy; CI = confidence interval; GG = International Society of Urological Pathology grade group; RS = risk score.

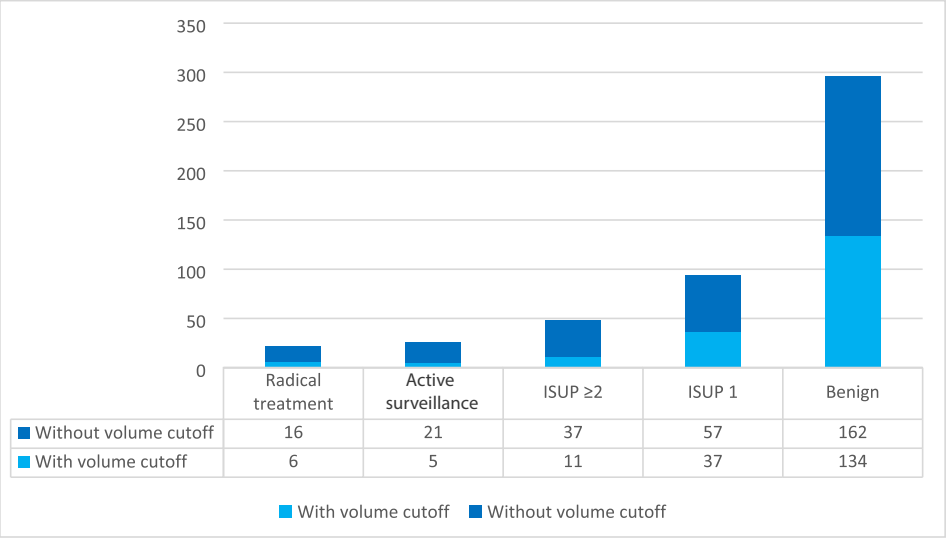

Fig. 2 – Treatment and biopsy results stratified by use of a volume cutoff for the Stockholm3 test. ISUP = International Society of Urological Pathology grade group.

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40.3–67.4%) with GG ≥2 disease who did not undergo radical treatment included five men (10.4%, 95% CI 1.2–6.3%) with a volume cutoff and 21 (43.8%, 95% CI 5.4–12.2%) without a volume cutoff. These men were followed according to an active surveillance protocol with a new MRI before biopsies within 1 yr.

When proceeding with biopsies only for patients without a volume cutoff, the number of GG 1 cases would be reduced by 37 (39.4%, 95% CI 20.1–49.5%). In addition, 182 overall biopsies (41.6%, 95% CI 37.0–46.2%) would be avoided at the expense of delaying a diagnosis in 11 men (6%, 95% CI 3.4–10.5%) with GG ≥2 disease in patients with a volume cutoff in their Stockholm3 test reports.

4. Discussion

This study demonstrates that for all patients with a positive Stockholm3 test and a negative MRI, biopsies can be safely omitted except for men without a volume cutoff in their Stockholm3 test reports. This strategy has a low risk of missing csPCa and reduces the number of nonsignificant cancers diagnosed and the number of biopsies performed.

Earlier research showed that the proportion of csPCa cases missed and biopsy procedures avoided depends on whether patients are biopsy-naïve or not [6–8]. Evidence is considered weaker for biopsy-naïve patients and stronger for patients with previous negative biopsies according to the EAU guidelines [1]. In our study, 96% of the patients were biopsy-naïve and the risk of csPCa in the overall group was still low. This demonstrates that for patients with a negative MRI, the Stockholm3 algorithm stratifies them to allow patients with a volume cutoff in their reports to avoid biopsies.

The number of biopsies avoided also depends on the PI-RADS threshold and the definition of csPCa. Variability in the definition of csPCa is large. We applied the same definition regardless of age, although it is relevant to discuss which cancers are clinically relevant for patients older than a certain age. The median age of 69 yr in our cohort is higher than in the studies included in a recent review applying the same definitions for PI-RADS and csPCa, which found that 30% of all biopsy procedures could be avoided while 11% of GG ≥2 cases would have been missed [6].

To help in deciding on when to perform prostate biopsies, multiple publications and several guidelines advise a combination of MRI findings and PSA-D [1,15,19]. Risk-adapted strategies are also available to aid in selecting patients for biopsies, in which family history and DRE are included in addition to PSA-D [16,17,20]. The Stockholm3 algorithm calculates the risk of having csPCa on the basis of levels of PSA and four other proteins, 101 genetic markers (single-nucleotide polymorphisms), family history, use of medication for benign prostatic hyperplasia, and previous biopsy. In addition, prostate volume and DRE are part of the recommendations on further follow-up.

The risk of csPCa in the group of patients without a volume cutoff in their reports was ~14% and is comparable to findings in a recent meta-analysis in which the risk of csPCa was 8% for biopsy-naïve men and 18% for men in intermediate-high and high PSA-D risk groups [15]. These risk levels support a strategy whereby biopsies are only performed in patients without a volume cutoff, leaving a risk of just 6% of detecting GG ≥2 disease in the remaining patients. However, looking at the clinical consequences, only ~6% of patients in the group without a volume cutoff went on to receive radical treatment. An individual risk assessment based on age group, comorbidities, and life expectancy can aid the decision on whether to perform biopsies for patients without a volume cutoff in their Stockholm3 test report.

In 2021 the definition of a positive Stockholm3 risk score was changed from ≥11% to ≥15% to correspond to a PSA level of 3.0 ng/ml [20]. This modification has been used in later publications [21]. We adhered to the original definition of a positive test (risk score ≥11%) as that was the definition used when our study was carried out. When using the new threshold of ≥15% for a positive Stockholm3 test in our group of patients, seven csPCa cases would have been missed, but only one of these had GG >2 disease. The health economic impact of not performing biopsies in patients with a negative MRI can be substantial. We report that combining the Stockholm3 test with a negative MRI leads to a ~40% reduction in both overdiagnosis and biopsy numbers, even when performing biopsies in patients without a volume cutoff in their Stockholm3 test report. This further reduces the already lower number of biopsies in previous studies reporting on the use of the Stockholm3 test [16]. Further studies are warranted to investigate the economic effect of this strategy.

The major strengths of our study are related to the data and study setting. The regular GP scheme in Norway and GPs' collaboration with the hospital cover nearly all men tested for PCa and includes the entire diagnostic pathway from the GP to the biopsy results. Since the data were collected retrospectively as outlined, we do not know the number of positive Stockholm3 tests that did not lead to further investigations via MRI. Thus, this patient cohort might represent a selection bias. Other limitations include the lack of long-term follow-up data; thus, the risk of developing csPCa during follow-up is unknown. It is known that MRI inter-reader reproducibility is moderate, even after introduction of PI-RADS v2 and multidisciplinary meetings with correlation and feedback [1]. For the men who did not undergo a prostate biopsy because the urologist considered there was low risk of csPCa, selection bias in this sense might have influenced the detection of csPCa. There is limited information on further follow-up for these patients. The study included mainly Scandinavian men; ongoing studies are validating the Stockholm3 test in a non-Scandinavian population.

The Stockholm3 algorithm provides a structured follow-up protocol for both GPs and urologists. For patients with a volume cutoff in their Stockholm3 report who do not undergo biopsy, a new Stockholm3 test after 2 yr is recommended. Additional PSA testing is not advised.

5. Conclusions

This study provides evidence that among patients with a positive Stockholm3 test and a negative MRI, prostate

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biopsies can be safely postponed for patients with a volume cutoff in the Stockholm3 test report. For patients without a volume cutoff in the Stockholm3 report, biopsies can be considered in a shared decision-making process. For the remaining patients, a Stockholm3 test after 2 yr is recommended.

Author contributions: Maria Nyre Vigmostad had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Vigmostad, Vinje, Kjosavik, Gilje, Skeie, Grönberg.
Acquisition of data: Kjosavik, Vinje, Vigmostad.
Analysis and interpretation of data: Vinje, Vigmostad, Kjosavik, Gilje, Skeie, Grönberg.
Drafting of the manuscript: Vigmostad, Vinje.
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