Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Audun Bakke Jensen

A Retrospective Follow-up Study of Patients with Negative Multiparametric Prostate MRI

Graduate thesis in Medicine
Supervisor: Kirsten Margrete Selnæs
Co-supervisor: Ingerid Skjei Knudtsen and Sverre Langørgen
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Contents

Abstract (Norwegian)

Bakgrunn: Det er ikke allment akseptert at det er trygt og ønskelig å avstå fra biopsi i tilfeller av negativ multiparametrisk MR (mpMR) av prostata hos biopsinaive menn. Denne studien er en retrospektiv oppfølgingsstudie av biopsinaive pasienter med negativ mpMR, der formålet er å undersøke den diagnostiske nøyaktigheten til mpMR samt om det finnes andre prediktorer for kreft.

Metode: Sykehusjournalene (2015-2022) til 101 pasienter som hadde gjennomgått mpMR-undersøkelse med PI-RADS score 1-2 fra 2015-2017 ble retrospektivt gjennomgått. Kliniske variabler fra den første mpMR-undersøkelsen og biopsien var samlet i tidligere studier. I denne studien ble oppfølgingsdata for nye henvisninger til MR av prostata samt biopsier av prostata innsamlet. For å beskrive kohorten ble det brukt generell deskriptiv statistikk, og negativ prediktiv verdi (NPV) ble utregnet med påvist signifikant kreft i løpet av oppfølgingsperioden som referansetest. Cox regresjonsanalyse ble brukt for å identifisere prediktorer for signifikant prostatakreft.

Resultater: 99 pasienter ble inkludert i dataanalysen. 69/99 pasienter gjennomgikk systematisk biopsi i sammenheng med den første mpMR-undersøkelsen. Etter oppfølgingsperioden hadde 11/99 pasienter blitt diagnostisert med signifikant prostatakreft (sPCa). Av disse fikk fem diagnosen i forbindelse med biopsi tatt etter den første mpMR-undersøkelsen, to ble først diagnostisert med insignifikant prostatakreft som så progredierte til sPCa under oppfølgingsperioden og fire pasienter som ikke ble biopsert i forbindelse med den første MR-undersøkelsen fikk påvist sPCa i løpet av oppfølgingsperioden. NPV for mpMR for sPCa etter oppfølgingsperioden var 88,9%, og kombinert med PSA-densitet (PSAD) <0,15 var NPV 95,1%. PSAD var en uavhengig prediktor for sPCa med hasard ratio 1.14 (1.07-1.21).

Konklusjon: Det er risiko for å gå glipp av tilfeller av signifikant kreft etter en negativ mpMR. PSAD er en signifikant prediktor for kreft og øker den diagnostiske nøyaktigheten til mpMR. Denne parameteren bør derfor bli vurdert sammen med mpMR i tilfeller hvor man vurderer nødvendighet av biopsi etter en negativ mpMR-undersøkelse.

Abstract (English)

Background: It is not generally acknowledged that it is preferable and safe to avoid biopsy in cases of negative multiparametric MRI (mpMRI) of the prostate in biopsy-naïve men. This study is a retrospective follow-up study of biopsy naïve patients with negative mpMRI assessing the diagnostic accuracy of mpMRI and evaluating other cancer predictors.

Methods: The hospital records (2015-2022) of 101 patients that had undergone mpMRI examination with a PI-RADS score of 1-2 from 2015-2017 were retrospectively reviewed. Clinical variables regarding the first mpMRI examination and biopsy were collected in earlier studies. In this study, follow-up data concerning new referrals to mpMRI, and biopsy of the prostate were collected. To describe the cohort general descriptive statistics were used, and the negative predictive value (NPV) was calculated with sPCa diagnosis during the follow-up period as the reference test. Cox regression analysis was used to identify predictors of significant prostate cancer.

Results: 99 patients were included in the final analysis. 69/99 patients underwent systematic biopsy in relation to the first mpMRI examination. After follow-up 11/99 patients had been diagnosed with significant prostate cancer (sPCa), of which five were diagnosed with sPCa in relation to the first mpMRI and biopsy, two were diagnosed with sPCa during follow-up after first being diagnosed with insignificant prostate cancer in relation to the first mpMRI, and four patients that were not biopsied in relation the first mpMRI were diagnosed with sPCa later in the follow-up period. PSA density (PSAD) was an independent predictor of sPCa with a hazard ratio of 1.14 (1.07-1.21). The NPV of sPCa after follow-up was 88,9%, and when combined with a PSA density <0.15 the NPV was 95.1%.

Conclusion: There is a risk of missing significant cancers if biopsy is not performed after a negative mpMRI examination. PSAD is a significant predictor of cancer and improves the diagnostic accuracy of mpMRI. It should therefore be assessed together with mpMRI-results when considering the necessity of biopsy in mpMRI negative men.

Introduction and Background

Prostate cancer is the cancer type with the highest incidence among men in Norway, constituting 26.5% of all male cancer cases between 2017 and 2021 (1). In 2020 prostate cancer was the cause of 9% of all cancer-related deaths, with 954 cases. The prognosis of a prostate cancer diagnosis has improved in the last decade. From a relative 5-year survival rate of 68.4% in the period 1992-1996, the survival rate from 2017-2021 was 95.5%.

In 2015, the diagnosis and treatment of prostate cancer were standardized in a clinical pathway in Norway (2). A clinical pathway is a system with deadlines for the diagnosis and treatment of patients with a certain disease. For a patient to start the clinical pathway for prostate cancer, a urologist must consider if there is sufficient suspicion of prostate cancer. The assessment is based on the prostate-specific antigen (PSA) level, the result of a digital rectal examination (DRE), and if there are signs of metastases. According to the clinical pathway, the diagnosis should then be verified by biopsy, preferably after a prebioptic MRI. Treatment of cancer disease is started depending on the histologic diagnosis and staging. The histological diagnosis is given based on the International Society for Urological Pathology (ISUP) grading system from 2014 (3), which categorizes prostate cancers in a Grade Group from 1-5. The staging of prostate cancer (PCa) is based on the Tumor Node Metastasis (TNM) classification system that categorizes cancer based on the site and size of the primary tumor, whether it has spread to local lymph nodes or metastasized (4). Depending on staging, risk stratification, comorbidities and expected duration of life, the patient may be kept under active surveillance or receive treatment in the form of surgery, radiation therapy and/or hormonal therapy or chemotherapy (2).

According to the current Norwegian guidelines, MRI is not regarded as sufficient to rule out prostate cancer, so there must always be taken biopsies (2). The European guidelines give a weak recommendation for not taking a biopsy if the MRI is negative and there is a low clinical suspicion of cancer (5). The evidence for the value of pre-biopsy MRI is good, mainly because of its high sensitivity and use in MRI-targeted biopsy (5, 6). There is however not a general consensus that it is safe and preferable to avoid biopsy in cases of a negative MRI (2, 5). Studies have shown that MRI has a high negative predictive value (NPV) and that there is potential to avoid a considerable number of unnecessary biopsies (7, 8). There have also been identified predictive factors that can help improve the diagnostic accuracy of MRI further. Of

these PSA density (PSAD) is the most studied, and has shown the best results (9). PSA density is the ratio between PSA and prostate volume.

Multiparametric MRI (mpMRI) is an MRI protocol where primarily T2-weighted, diffusion-weighted and dynamic contrast-enhanced images are combined to make a detailed volumetric image of the entire prostate gland (10). In biparametric MRI (bpMRI) only T2-weighted and diffusion-weighted images are combined. bpMRI is the MRI protocol that is mostly used for prostate cancer diagnostics in Norway today. Both mpMRI and bpMRI will be labeled as mpMRI in this thesis. When interpreting and reporting mpMRI and bpMRI it has become standard to use the Prostate Imaging Reporting and Data System (PI-RADS) (10). PI-RADS was created to standardize the acquisition, interpretation, and reporting of mpMRI examinations by scoring lesions from 1-5 on the probability of clinically significant cancer. A PI-RADS score of 1 indicates a very low probability of significant cancer, and 5 a very high probability of cancer. A PI-RADS score of <3 is generally regarded as negative/non-significant cancer. PI-RADS version 1 was introduced in 2012, and version 2 in 2015. Version 2.1 was introduced in 2019 and is the PI-RADS version in use today (11).

Transrectal ultrasound (TRUS) guided biopsy is the standard biopsy method in use in the world today. The interest in MRI-targeted biopsy has increased after showing good results compared to TRUS (12), and is recommended used together with systematic TRUS biopsy in the European guidelines (5). Biopsy has associated risks of complications such as hematuria, hematospermia, pain, and urinary retention (13). The prevalence of LUTS (lower urinary tract symptoms) after TRUS biopsy is as high as 25%. There is also an increased risk of infections, with sepsis being one of the severe complications seen (13). Infections with antibiotic-resistant bacteria after a prostate biopsy is an increasing problem (13, 14).

In 2021 Krüger-Stokke et al. published an article where TRUS biopsy after mpMRI was used to evaluate the diagnostic precision and quality of mpMRI (15). 101 of the patients had a negative mpMRI, and of these, about 2/3 were biopsied. Of the biopsied patients, five with a negative mpMRI were diagnosed with significant prostate cancer (ISUP Grade Group >1). Because not all patients underwent biopsy and systematic biopsy is not a perfect reference test, it is of interest to do a follow-up study of these patients. It is unknown how many of the un-biopsied patients were false negatives, and it is possible that the TRUS biopsy didn't detect all cancer cases in the biopsied group. With follow-up data, one can better estimate the

true clinical rate of cancer when mpMRI is negative and find other predictors of cancer in the population.

Objectives

This retrospective follow-up study of 101 patients with PI-RADS 1-2 aims to give better insight into the diagnostic accuracy of mpMRI and evaluate other predictors of cancer. More specifically we evaluate:

- New referrals and cancer diagnoses of PI-RADS 1-2 patients in an approximately 5–7-year period following the first mpMRI examination.
- The hazard ratio of potential cancer predictors (age, PSA, and PSAD).
- The NPV of mpMRI using cancer status after follow-up as the reference test
- A reassessment of the initial mpMRI, and comparison with the second mpMRI, in patients diagnosed with significant prostate cancer after the second mpMRI.

Patients and Methods

Study Population

The study population is a subgroup of patients originally part of the prospective study by Krüger-Stokke et al. (15). The study population of the prospective study were 210 biopsy-naïve men with elevated PSA and/or abnormal DRE that from 2015 to 2017 were enrolled and underwent mpMRI (multiparametric-, not biparametric MRI). Patients with positive mpMRI were randomized to receive either only TRUS or both MRGB (MR-guided in-bore biopsy) and subsequent TRUS, to evaluate mpMRI and MRGB as tools in prostate cancer diagnostics. According to the study protocol, patients with negative mpMRI should undergo TRUS biopsy, but as previously mentioned, biopsy was deferred for a significant proportion of participants.

This study is a retrospective follow-up study looking at the 101 patients that had a negative mpMRI (PI-RADS 1-2) in the study by Krüger-Stokke et al. (labeled as MRGB study in figures). A flowchart of the study design is shown in Figure 1. Two patients were excluded

from the analysis, one because of withdrawn consent and the other because of having undergone a prostate biopsy before the study period.

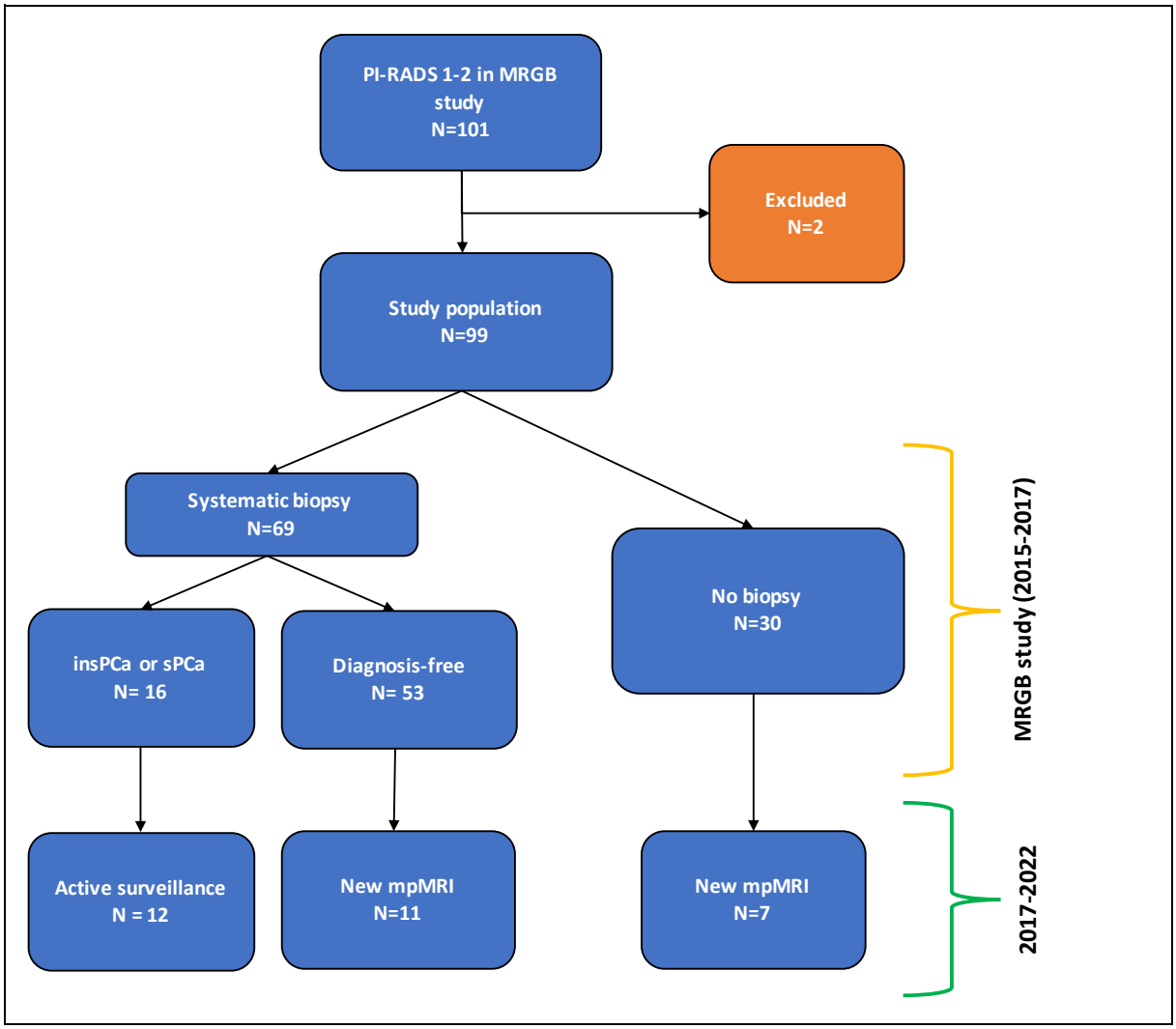

Figure 1: Flowchart of study design. Diagnosis-free = prostate cancer diagnosis-free; sPCa = significant cancer; insPCa = insignificant cancer; mpMRI = multiparametric MRI.

Data Collection

The hospital records of the included patients from the time of referral to the hospital (2015-2017) until September 2022 were reviewed. The data collected comes from the hospital records connected to St. Olav´s Hospital, Norway. The patients are also part of the Digitalt liv retrospektiv (DLR) cohort (identifier REK2017/576). Because of this, relevant clinical data regarding the first mpMRI and subsequent biopsy and treatment had already been collected from hospital records. The DLR data was used as a basis for the collection of data concerning

new referrals to prostate cancer diagnosis. It was also checked in the hospital records if patients had died or moved to another part of the country.

Clinical variables that already were collected and later used in the analysis were age at first mpMRI, the date and value of two PSA-tests before the first biopsy, the date and result of the first mpMRI (PI-RADS score, prostate volume, PSAD), date and results from the first biopsy, and what treatment the patients received. Clinical variables collected as part of this study were dates and results from new mpMRIs and biopsies of the prostate, PSA data in relation to the second mpMRIs, and data concerning new diagnoses of prostate cancer.

An experienced radiologist, S. Langørgen, reassessed and compared the mpMRIs of the patients diagnosed with sPCa after a referral to a new mpMRI as well as the patients in active surveillance where cancer had progressed from insignificant to significant. As part of the reassessment the radiologist evaluated if the cancer lesions only could be seen on the second mpMRI, or if cancer suspicious lesions had been overlooked during the first examination.

Outcome Measures and Statistics

The primary outcome was whether biopsy-naïve patients had been diagnosed with significant prostate cancer in the time after a negative mpMRI till the end of the follow-up period, set to 30. September 2022. Patients who had undergone a new prostate mpMRI because of suspicion of cancer were classified as a new referral for diagnosis of prostate cancer. Pathology results were reported as negative, insignificant prostate cancer (insPCa) or significant prostate cancer (sPCa). sPCa was defined as ISUP Grade Group ≥ 2 (Gleason score $\geq 3 + 4$). This is the same definition as used in the study by Krüger-Stokke et al. (15). Any cases of prostate cancer not labeled as Gleason score $\geq 3 + 4$ were reported as insPCa.

To describe the data, general descriptive statistics were used (median, range, number). The negative predictive value (NPV) was calculated to evaluate the diagnostic performance of mpMRI and mpMRI combined with PSAD. The negative predictive value was calculated by dividing the number of true negatives by the total test negatives. To calculate confidence intervals for NPVs the binomial test was used. Uni- and multivariable Cox regression analysis was used to identify predictors of sPCa, and whether they were independent. The variables included were age, PSA, and PSAD, and all variables were analyzed as continuous variables. PSAD was multiplied by 100 in the analysis to make each step 0.01 ng/ml/cc. The survival

time was defined as the number of months between the date of the first mpMRI to the date of the examination (often biopsy) where the cancer was detected. All statistical analyses were performed using IBM SPSS version 28.0.1.0 or R (16). A p-value of < 0.05 was defined as a statistically significant result.

Ethics

The study was carried out under an existing approval by The Regional Committee of medical and Health Ethics, Central Norway (identifier REK2013/1869). The patients have given written informed consent.

Results

By the end of the follow-up period, all 99 patients lived in the county covered by the hospitals whose medical records data were collected from. One patient had died during the follow-up period, but not from prostate cancer.

The median (range) follow-up time of PCa diagnosis-free patients was 75.6 (49.5-91.7) months. If excluding the patient that died during follow-up, the minimum follow-up time was 60 months. In relation to the first mpMRI, 69 patients underwent systematic TRUS biopsy. Of these, five were diagnosed with significant cancer (sPCa) and 11 with insignificant cancer (insPCa). After the follow-up period, of 99 patients two insPCa cases had progressed to sPCa, and four previously PCa diagnosis-free patients had been diagnosed with sPCa, bringing the total number of patients with sPCa to 11. One patient was diagnosed with insignificant cancer after TUR-P, and since two cases of insPCa had progressed to sPCa, the total insPCa cases were 10 after follow-up. The clinical characteristics of the different groups after follow-up are shown in Table 1.

The median (range) survival time for patients diagnosed with sPCa was 12.4 months (0.1-65.8). On univariable Cox regression analysis age and PSA was not predictors of sPCa, while PSAD was a significant predictor. Multivariable Cox regression analysis showed that PSAD was a significant independent predictor ($p<0.001$) of sPCa with a hazard ratio of 1.14. Age and PSA were not predictors of sPCa as shown in Table 2.

Table 1

Clinical characteristics of the study population

Variable	Highest PCa diagnosis after follow-up			
	PCa diagnosis-free	insPCa	sPCa	All
N	78	10	11	99
Age (years)	65 (45-76)	66 (55-72)	65 (52-74)	65 (45-76)
PSA (ng/ml)	6.1 (0.8-16.4)	6.2 (4.6-13.0)	5.3 (4.0-10.4)	6.1 (0.8-16.4)
Prostate volume (cc)	60 (30-203)	65 (39-169)	31 (15-57)	57 (15-203)
PSAD (ng/ml/cc)	0.10 (0.03-0.32)	0.12 (0.05-0.25)	0.15 (0.08-0.42)	0.11 (0.03-0.42)

Descriptive statistics are median (range). All parameters are from the time of the first mpMRI. PCa = prostate cancer; sPCa = significant prostate cancer; insPCa = insignificant prostate cancer; mpMRI = multiparametric MRI. PSA = prostate-specific antigen; PSAD = PSA density.

Table 2

Results of multivariable Cox regression analysis

Variable	HR	95% CI	p-value
Age (years)	9.57	0.85-1.08	0.462
PSA (ng/ml)	9.67	0.77-1.22	0.777
PSAD*100 (ng/mm/cc)	1.14	1.07-1.21	<0.001

PSA = prostate-specific antigen; PSAD = PSA density; HR = hazard ratio; CI = confidence interval.

Men Referred to a New mpMRI

Of the 83 men previously not diagnosed with cancer, 18 were referred to at least one new mpMRI during the follow-up period. Of the 18 patients, seven were not previously biopsied. All 18 patients were referred with the main reason being an elevated PSA. Of the 18 patients referred to a new mpMRI, 12 underwent a subsequent biopsy whereof five were biopsy naïve. Three patients were diagnosed with PCa; two cases of insPCa, and one of sPCa. One of the patients with a negative biopsy had a positive biopsy showing sPCa on a later biopsy. The two cases of insPCa were found to be sPCa on later histology. All four patients diagnosed with sPCa during the follow-up period did not undergo a biopsy in relation to the first mpMRI. The clinical characteristics of the patients referred to a second mpMRI, grouped after the highest diagnosis after follow-up, are shown in Table 3.

Table 3

Clinical characteristics of men referred to a new mpMRI

Variable	Highest PCa diagnosis after follow-up		
	PCa diagnosis-free	**sPCa**	**All**
N	14	4	18
Months between mpMRIs	43 (24-74)	31 (27-46)	38 (24-74)
Age (years)	62 (53-71)	56 (52-65)	60 (52-71)
PSA-1 (ng/ml)	6.0 (3.7-9.5)	4.7 (4.0-7.6)	5.5 (3.7-9.5)
PSA-2 (ng/ml)	8.8 (5.0-15.6)	6.1 (4.9-7.3)	7.7 (4.9-15.6)
PSA change (ng/ml)	2.6 (0.3-8.0)	1.8 (-2.7-2.5)	2.3 (-2.7-8.0)
Prostate volume-1 (cc)	58 (39-93)	29 (15-44)	56 (15-93)
Prostate volume-2 (cc)	81 (42-120)	31 (21-39)	68 (21-120)
Prostate volume change (cc)	13 (-10-40)	3 (-5-6)	6 (-10-40)
PSAD-1 (ng/ml/cc)	0.09 (0.05-0.17)	0.15 (0.11-0.33)	0.10 (0.05-0.33)
PSAD-2 (ng/ml/cc)	0.11 (0.08-0.18)	0.20 (0.13-0.32)	0.13 (0.08-0.32)
PSAD change (ng/ml/cc)	0.02 (-0.03-0.09)	0.02 (-0.01-0.08)	0.02 (-0.03-0.09)

Descriptive statistics are median (range). PCa = prostate cancer; sPCa = significant prostate cancer; mpMRI = multiparametric MRI. PSA = prostate-specific antigen; PSAD = PSA density. PSA-1, Prostate volume-1, and PSAD-1 are measurements from the first mpMRI. PSA-2, Prostate volume-2, and PSAD-2 are measurements from the second mpMRI.

Patients in Active Surveillance

12 patients followed an active surveillance protocol after being diagnosed with PCa in relation to the first mpMRI and biopsy. Of the 12 patients, one had been diagnosed with sPCa and 11 with insPCa. After the follow-up period, two cases of insPCa had progressed to a sPCa, and the rest of the PCa-cases had not progressed.

A flowchart of the outcomes in the study population is shown in Figure 2.

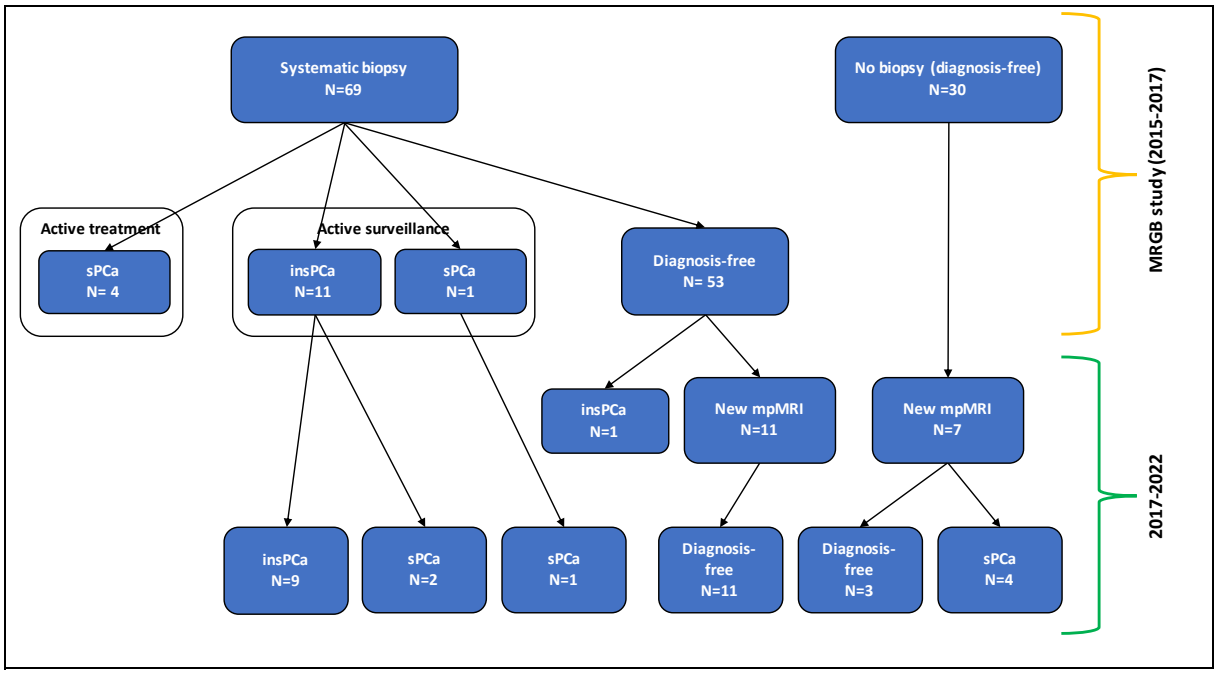

Figure 2: Flowchart of outcomes after follow-up. Diagnosis free = prostate cancer diagnosis-free; sPCa = significant cancer; insPCa = insignificant cancer; mpMRI = multiparametric MRI.

Second mpMRI Results and Reassessment of mpMRIs

Table 4 shows the PI-RADS scores of the 30 patients that had at least one new mpMRI in the follow-up period. The median (range) number of months between the first and second mpMRIs was 43 (13-74). All patients with a PCa diagnosis after follow-up had a PI-RADS score of 3 or higher on the second mpMRI. One PCa diagnosis-free patient after follow-up had PI-RADS 3 on his second mpMRI. The relationship between PI-RADS score and PCa diagnosis is shown in Table 4.

The first and second mpMRI of the four patients that were diagnosed with sPCa during follow-up, and the two patients in active surveillance with a progression from insPCa to sPCa, were reassessed and compared by a radiologist. For three patients, the first mpMRI was interpreted as cancer-suspicious in this retrospective assessment. One patient had minimal signs of cancer on the first mpMRI when reassessed, and in two cases the cancer-suspicious changes in the second mpMRIs seemed to be new lesions.

Table 4

Cross-tabulation of PI-RADS and PCa diagnosis after follow-up

		Highest PCa diagnosis after follow-up			Total
		PCa diagnosis-free	insPCa	sPCa	
	1	6	5	0	11
	2	7	4	0	11
PI-RADS in second mpMRI	**3**	1	0	3	4
	4	0	0	3	3
	5	0	0	1	1
Total		14	9	7	30

PCa = prostate cancer; sPCa = significant prostate cancer; insPCa = insignificant prostate cancer; mpMRI = multiparametric MRI.

Negative Predictive Value

The negative predictive value of the first mpMRI with PI-RADS 1-2 with sPCa diagnosis after follow-up as the reference test is 88.9% (Table 5). When using a PSAD score of <0.15 together with PI-RADS 1-2 as the predictor, the negative predictive value for the population is 95.1%.

Table 5

NPV with and without PSAD thresholds

	Highest PCa diagnosis after follow-up		
	sPCa diagnosis-free	sPCa	NPV (95% CI)
PSAD < 0.15	78	4	0.951 (0.880-0.987)
Without PSAD	88	11	0.889 (0.810-0.943)

sPCa = significant prostate cancer; NPV = negative predictive value; PSAD = prostate-specific antigen density; CI = confidence interval.

Discussion

Prebiopsy multi-parametric mpMRI is a part of the clinical pathway for prostate cancer in Norway and is also recommended in the European guidelines (2, 5). The Norwegian guidelines say that all patients should undergo a biopsy to exclude cancer, but in a real-world setting, a substantial percentage of patients do not. For reasons such as declining PSA, comorbidities, and personal reasons, 30/99 (30.3%) patients did not undergo a biopsy after a negative mpMRI in our study population. 4/30 (13.3%) of these patients were diagnosed with sPCa during follow-up, showing that there is a risk associated with avoiding biopsy after a negative mpMRI. The four patients were all diagnosed with GG2 cancers and underwent subsequent radical prostatectomy. There is no sign that the patients had worse outcomes because of a delayed diagnosis than the patients biopsied after the first mpMRI.

There were no new cases of prostate cancer in the group of patients that had an initial negative mpMRI and negative systematic biopsy. This indicates that the current recommendation of mpMRI and biopsy is good at detecting cancer.

NPV is an important parameter to evaluate when assessing the clinical value of prostate mpMRI and the risks of avoiding biopsy in cases of a negative mpMRI. There are inherent difficulties in calculating a true NPV, which has been pointed out in a systematic review and Meta-analysis where the NPV was shown to vary depending on the prevalence of cancer in the study populations, study designs, and definitions of sPCa and negative mpMRI (17). In the study by Krüger-Stokke et al. (15), the patients that did not undergo the reference test (TRUS-biopsy) were excluded from the analysis of NPV, as is normal. This method will however potentially over- or underestimate the NPV. In our follow-up study, we have included the patients that did not undergo biopsy with the reasoning that the patients with undetected significant cancer would have been readmitted to the hospital during the follow-up period. After follow-up, there were a total of 11/99 cases of significant cancer which resulted in a NPV of 88.9%. That is slightly lower than the 92% that was reported in the study by Krüger-Stokke et al. and supports the notion that NPV is overestimated with many study designs.

PSAD has in a meta-analysis and systematic review from 2020 been shown to be a significant predictive factor to rule out significant cancer in patients with negative mpMRI (9). The hazard ratio (HR) of PSAD in our study was 1.14 (95% CI 1.07-1.21). The PSAD value was analyzed as PSAD*100 in the Cox regression analysis, so each step is 0.01 ng/ml/cc. The HR could therefore be interpreted as that the risk over a time period associated with having a 0.01 ng/mm/cc higher PSAD value than someone else is 1.14 or 14%. Furthermore, a difference of for instance 0.05 ng/mm/cc will give an HR of $1.14^5 = 1.93$. The HR of 1.14 in our study is not within the confidence interval of a follow-up study by V. Panebianco et al. with 659 patients at risk where the hazard ratio was found to be 7.57 (95% CI 2.73-21) (18). A reason for this difference can be that the PSAD-variable was used differently in the studies. This is however not certain because the interpretation of PSAD in the Cox regression analysis is not stated in the article. When making the PSAD value discrete (over or under 0.15) the HR is 11.69 in our analysis, which is within the confidence interval of the study by V. Panebianco et al.

Age and PSA were not independent predictors of cancer in our analysis. This is not in accordance with the results from V. Panebianco et al.´s study where both PSA and age were significant predictors, with hazard ratios of respectively 1.21 and 0.93 (18). In the systematic review and metanalysis from 2020, PSA was shown to be a predictive factor in two out of five studies, while age was a predictive factor in one study (9). In multivariate analysis both PSA and age showed contradictory results according to the review.

When calculating NPV by combining a PSAD cut-off of <0.15 with a negative mpMRI, 82/99 patients were included and only four patients had sPCa after follow-up with a resulting NPV of 95.1%. Our data therefore indicate that by using PSAD together with mpMRI you can still avoid a substantial number of biopsies but with a reduced risk of missing significant cancers compared to using mpMRI alone.

All the patients not diagnosed with cancer in relation to the first MRI but who received a cancer diagnosis by September 2022, had a PI-RADS score of >2 on the second mpMRI. In this sense, no cancer stayed silent. The reassessment and comparison of the first and second mpMRIs of patients diagnosed with sPCa further showed that some four of the six significant cancers in retrospect could have been detected on the first mpMRI and therefore weren’t

silent. This finding also highlights the problem of inter- and intra-reader reproducibility of mpMRI and PI-RADS, as well as the importance of experience (19).

This study has some important limitations. Because of the design of the study, with no pre-follow-up protocol, the only follow-up data on some patients is the absence of a referral to the urology department at the hospital, and that they still live in the study county. There is therefore a risk that significant cancers haven't been detected. New referrals and cancers could also have been missed if patients have seen a private urologist. However, a private urologist would in most cases of cancer suspicion refer the patient to St. Olav´s Hospital where the health records have been collected. The long follow-up time of a minimum of 50 months is a strength of the study. Another limitation is that some patients referred to a new diagnosis used medication that lowers PSA, the PSA levels should therefore be interpreted with that in mind.

Conclusion

With a NPV of 88.9% after follow-up, this study supports the evidence that mpMRI has a relatively high NPV but that some significant cancers are missed if avoiding biopsy in cases of a negative mpMRI. When a negative mpMRI is combined with PSAD <0.15 the performance of mpMRI improves further, and PSAD was an independent predictor of cancer in our population. When considering the necessity of taking biopsies in cases of a negative mpMRI our data indicate that adding PSAD to the evaluation is an effective measure to reduce the risk of missing significant cancer.

Acknowledgments

My supervisors have been crucial for the completion of this thesis, and I am grateful to them for sharing their knowledge and helping me in this learning process. Senior engineer Torill Eidhammer Sjøbakk was very helpful in getting me started with the data collection for the project. Associate professor and statistician Øyvind Salvesen´s advice on what statistical methods to use and how to make our data fit the chosen models was of big help and is greatly

appreciated. I would also like to thank Professor Tone Frost Bathen at the Department of Circulation and Medical Imaging who introduced me to the thesis project and my supervisors.

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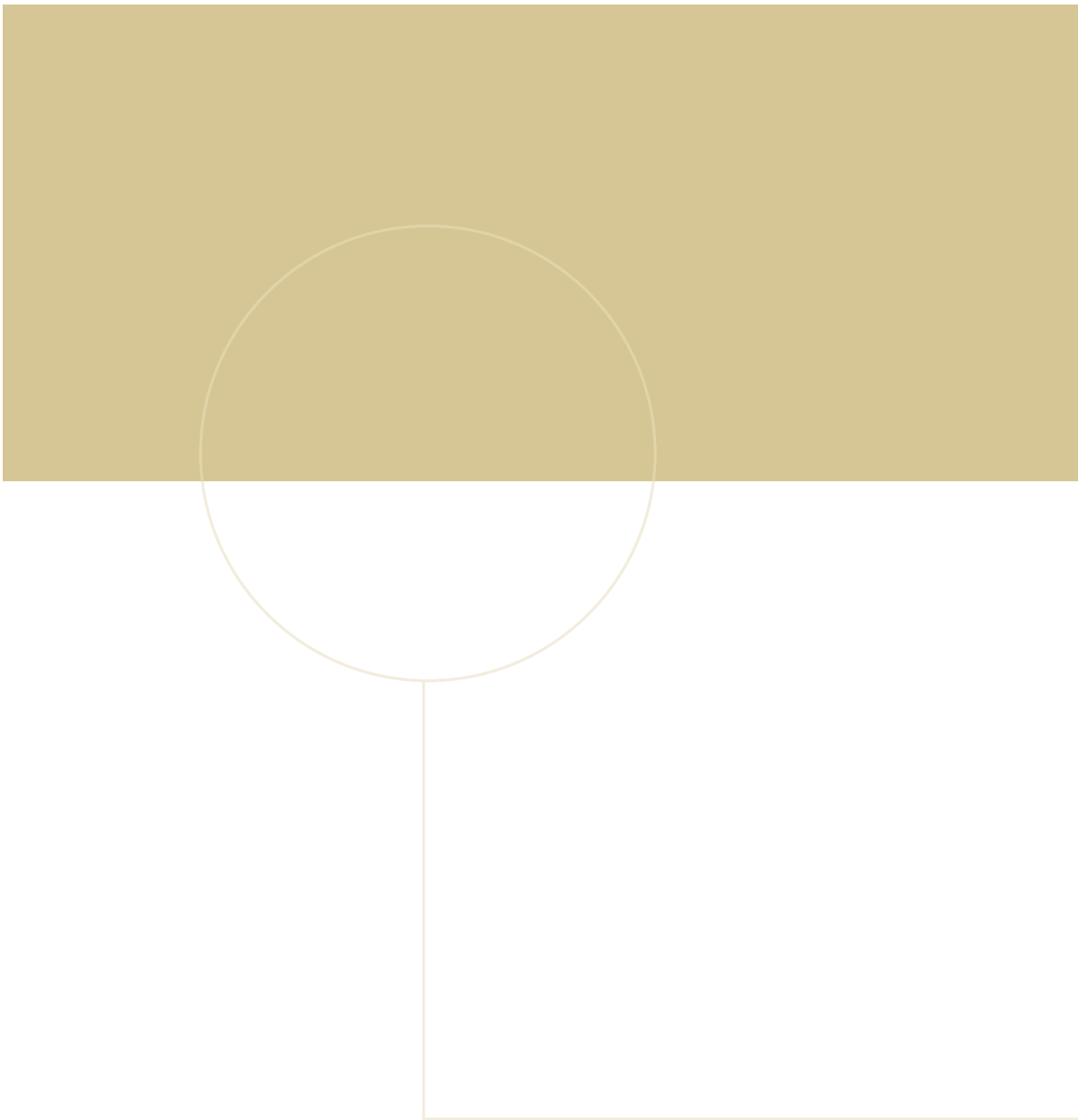

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