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Predictors of upgrading from low-grade cancer at prostatectomy in men with biparametric magnetic resonance imaging

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Introduction Prostate-specific antigen (PSA) density has previously been identified as a predictor of histological upgrading at radical prostatectomy, but how information from pre-treatment biparametric magnetic resonance imaging (bpMRI) contributes needs further clarification. The objective of this register-based study was to identify predictors of upgrading at prostatectomy in men with Grade group (GG) 1 and pre-treatment bpMRI.

Material and methods This single-center study included men with GG 1 cancer on prediagnostic biopsy, who underwent bpMRI and robotic-assisted radical prostatectomy (RARP) between March 2014 and September 2019. We estimated logistic regression models to explore predictors for upgrading. The explored potential predictors were age, PSA density, tumor stage and Prostate Imaging Reporting and Data System (PI-RADS) score (dichotomised 1–3 versus 4–5).

Results Upgrading was observed in 56% (73/130) of the men. PSA density was the only significant predictor for upgrading (unadjusted OR = 1.7, 95% CI 1.2; 2.4 adjusted OR = 1.7, 95% CI 1.2; 2.5). The probability of upgrading was lower for men with a PIRADS 1–3 than for PIRADS 4–5, but the difference was not statistically significant (adjusted OR 0.4, 95% CI 0.2; 1.1, p = 0.082). Among men with PI-RADS 1–3, the probability increased with increasing PSA density (p = 0.036). With PI-RADS 4–5 the probability of upgrading was high over the entire PSA density range.

Conclusions PSA density is a clinically important factor to predict upgrading from GG1 when bpMRI shows PI-RADS 1–3. In men with PI-RADS 4–5 on bpMRI, the probability of an undetected GG 2–5 cancer is high regardless of the PSA density.

Key Words: histological upgrading ‹› biparametric magnetic resonance imaging ‹› robotic-assisted radical prostatectomy

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INTRODUCTION

The clinical diversity of localized prostate cancer often makes it difficult to decide how best to treat an individual patient. Clinically significant prostate cancers eventually may cause local symptoms, spread to other organs and lead to death. Opposed to this, insignificant, low-grade, prostate cancers progress over decades, or not at all, and the patients die of other causes. Thus, for these men, guidelines recommend monitoring rather than treatment [1]. Despite this, many men with low-grade prostate cancer are still offered either radiation therapy or surgery. One reason may be that some men that we presume have a low-grade cancer, actually harbour an undetected high-grade cancer, and that we have insufficient models to predict this [2].

The International Society of Urological Pathology (ISUP) recommends that prostate cancer histology is categorized into five grade groups (GG 1–5) [3]. There is no consensus on how to define clinically significant prostate cancer, but one common definition is grade group 2–5 (previously Gleason score 7–10) [4]. According to this definition, GG 1 (previously Gleason score 6) represents clinically insignificant cancer. GG on biopsy does, however, often not accurately represent the GG of the entire primary tumor. For men with GG 1 on biopsy, the cancer is upgraded in the final histology after radical prostatectomy in more than one third of the cases [5, 6, 7]. This clearly is of concern for men with a presumed GG 1 cancer who consider opting for active surveillance rather than having upfront surgery or radiotherapy.

One clinically important predictor of histological upgrading is prostate-specific antigen (PSA) density, i.e. the serum PSA value divided by the prostate volume [5, 8]. Findings on prostate magnetic resonance imaging (MRI) are also associated with histological tumor grade [9–12]. Prostate Imaging-Reporting and Data System (PI-RADS) is the method of choice for evaluation of the prostate gland on MRI [13, 14]. Although the PI-RADS system is based on multiparametric MRI, it can also be applied on biparametric MRI (bpMRI), a protocol without dynamic contrast enhancement [15, 16]. BpMRI has detection rates comparable with multiparametric MRI. It is less time-consuming and therefore more cost-effective [9], and is increasingly used to assess men with raised PSA values.

In previous studies of the association between MRI findings and prostate cancer grade, a protocol with dynamic contrast enhancement was used [11, 12, 17]. As MRI without contrast is gaining a larger place in prostate cancer diagnostics, it is essential to establish how findings on bpMRI should affect clinical decision-making for men who consider active surveillance.

We therefore designed the present study to identify predictors of upgrading at radical prostatectomy in men with GG1 prostate cancer who have had a pre-treatment bpMRI, and to explore the association between PSA density and the probability of upgrading in men with versus without a suspicious tumor on the bpMRI.

MATERIAL AND METHODS

Study design

This was a single-center, observational study.

Study population

Between March 2014 and September 2019, 1049 patients underwent robotic-assisted radical prostatectomy (RARP). All patients were included in a quality register. Among these, all men with GG on initial biopsy and bpMRI before biopsy were included in the study, a total of 130. Both patients diagnosed with targeted biopsy and patients diagnosed with systematic biopsies were included. Among these, 84 men had systematic, transrectal biopsies, 15 patients systematic, transperineal biopsies and 28 targeted biopsies. For three men, information about how the biopsies were performed are missing.

Clinical and histological data

The clinical data included age, PSA, PSA density, tumor stage on bpMRI, PI-RADS score, GG on pre-treatment biopsy, and GG and stage (pT) in the prostatectomy specimen. GG was assessed by trained uropathologists. PSA density was calculated as last available preoperative PSA value divided by the prostate volume as estimated based on MRI measurements (length x width x height x ϖ/6).

Biparametric magnetic resonance imaging

At the study center over 800 biparametric prostate MRIs are performed each year for diagnostic purpose, and all patients in the present study had a bpMRI before biopsy. BpMRI was performed with 1.5 Tesla (Phillips Achieva) resolution without endorectal coil. The protocol included T2-weighted and diffusion-weighted images. All bpMRIs were classified by dedicated uroradiologists according to PI-RADS (version 1.0 and 2.0). For this study, the most experienced uroradiologist re-evaluated all bpMRIs for staging purposes.

Statistical analysis

Clinical characteristics were described by medians, min and max values, means, and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. Unadjusted and adjusted logistic regression models were used to assess the preoperative factors age, PSA density, PI-RADS (1–3 versus 4–5) and MRI stage (T1–2 versus T3a or T3b) as predictors for the outcome measure: histological upgrading to GG 2–5 in the prostatectomy specimen. The small number of patients with PI-RADS 1–3 justified dichotomization of these variables for logistic regression analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The association between PSA density and the probability of upgrading among patients with PI-RADS 1–3 and PI-RADS 4–5 on MRI was explored by logistic regression model with PSA density, PI-RADS and the interaction between these two. Given the limited sample size and the distribution of the outcome measure, the number of preoperative factors that were included in the regression analysis had to be restricted. We chose to include PSA density in the model, but excluded PSA, as previous studies have unanimously shown that PSA density is the better marker of the two.
All tests were two-sided, and results with p-values <0.05 were considered statistically significant. Statistical analyses were done with SPSS v26.

Table 1. *Clinical data for patients with GG 1 and GG 2–5 after prostatectomy, N = 130*

Covariate	Total	GG 1 (N = 57)	GG 2–5 (N = 73)
Age, years			
Median (min–max)	65 (44–79)	63 (44–76)	66 (46–79)
Mean (SD)	63.9 (6.6)	63.2 (6.5)	64.4 (6.6)
PSA, ng/mL			
Median (min–max)	10.0 (2.2–56.7)	9.7 (3.9–20.8)	10.9 (2.2–56.7)
Mean (SD)	11.2 (6.5)	9.7 (3.4)	12.4 (7.9)
PSA density, ng/mL/cm^3			
Median (min-max)	0.19 (0.04–1.22)	0.17 (0.06–0.61)	0.22 (0.04–1.22)
Mean (SD)	0.23 (0.15)	0.19 (0.09)	0.26 (0.18)
PI-RADS score			
≤3, n (%)	27 (20.8)	16 (28.1)	11 (15.1)
4 or 5, n (%)	103 (79.2)	41 (71.9)	62 (84.9)
Tumor stage on MRI			
T1–2, n (%)	102 (78.5)	48 (84.2)	54 (74.0)
T3a, n (%)	25 (19.2)	9 (15.8)	16 (21.9)
T3b, n (%)	3 (2.3)	0	3 (4.1)
pT			
T2, n (%)	83 (63.8)	42 (73.7)	41 (56.2)
T3a, n (%)	44 (33.8)	14 (24.6)	30 (41.1)
T3b, n (%)	3 (2.3)	1 (1.8)	2 (2.7)

GG – grade group; N – number of patients; SD – standard deviation; PSA – prostate-specific antigen; PSA density – PSA divided by prostate volume; PI-RADS – Prostate Imaging Reporting and Data System; MRI- magnetic resonance imaging

RESULTS

The median age of the 130 men included was 65 years (range 44–79 years), their median PSA 10.0 ng/mL (range 2.2–56.7 ng/mL) and their median PSA density 0.19 ng/mL/cm^3 (range 0.004–1.22 ng/mL/cm^3). On bpMRI, 27 men (20.8%) had PIRADS 1–3 and 102 (78.5%) were staged to have T1 or T2 tumors. The final histology stage on the prostatectomy specimen was T2 in 83 (63.8%) of the men (Table 1).
Upgrading from GG 1 to GG 2–5 was observed in more than half of the patients (56%). The characteristics of those who were upgraded versus those who were not are presented in Table 1. PSA density was the only analyzed preoperative factors that significantly predicted upgrading in both unadjusted and adjusted logistic regression (unadjusted OR = 1.7, 95% CI 1.2; 2.4 and adjusted OR = 1.7, 95% CI 1.2; 2.5, Table 2). The association between

Table 2. *Predictors for upgrading from biopsy GG 1 to GG 2–5 in radical prostatectomy specimens from 130 men, results of unadjusted and adjusted logistic regression*

Covariate	Unadjusted model		Adjusted model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.03 (0.98; 1.08)	0.308	1.01 (0.96; 1.07)	0.688
PSA density[1]	1.65 (1.15; 2.36)	0.006	1.72 (1.19; 2.49)	0.004
PI-RADS				
1–3	0.46 (0.19; 1.08)	0.073	0.43 (0.17; 1.11)	0.082
4 or 5 – ref.	1		1	
Tumor stage on MRI				
T2 – ref.	1	0.163	1	0.240
T3a+T3b	1.88 (0.78; 4.5)		1.75 (0.69; 4.4)	

[1]OR for 0.1 ng/ml/cm^3 increments
GG – grade group; PSA – prostate-specific antigen; PSA density – PSA divided by prostate volume; PI-RADS – Prostate Imaging Reporting and Data System ; OR – odds ratio; CI – confidence interval

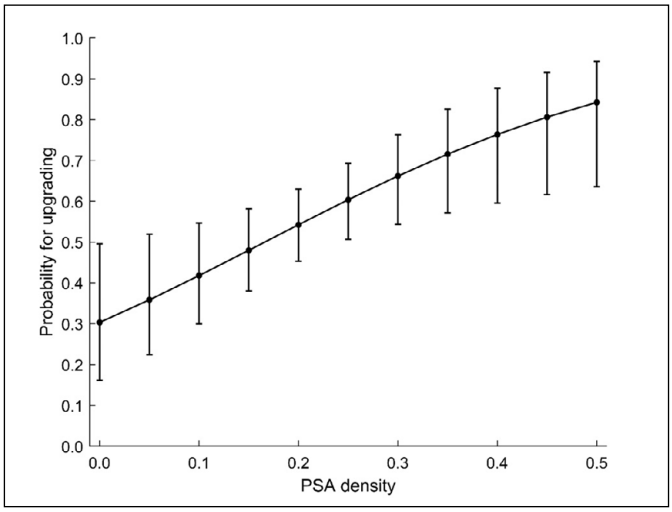

Figure 1. *The association between PSA density and the probability for upgrading from biopsy GG 1 to GG 2–5 in radical prostatectomy specimens from 130 men.*

GG – grade group; PSA – prostate-specific antigen; PSA density – PSA divided by prostate volume

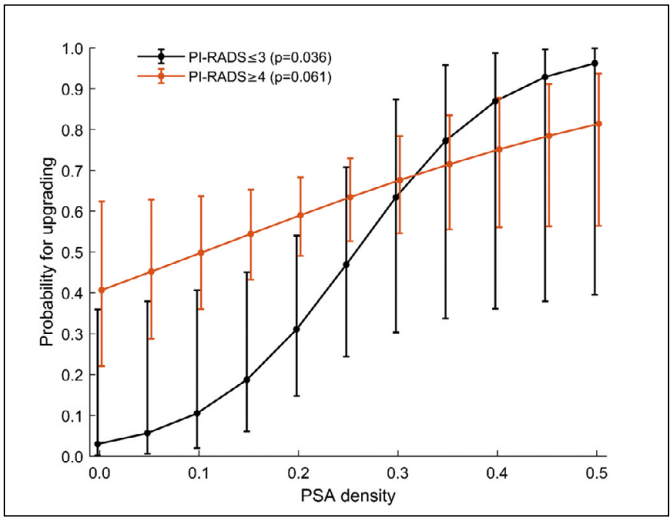

Figure 2. *The association between PSA density and the probability of upgrading from biopsy GG 1 to GG 2–5 in the radical prostatectomy specimen stratified by PI-RADS 1–3 and PI-RADS 4–5.*

GG – grade group; PSA – prostate-specific antigen; PSA density – PSA divided by prostate volume; PI-RADS – Prostate Imaging Reporting and Data System

PSA density and the probability of upgrading is illustrated in Figure 1. The probability of upgrading was about half as high for men with a PIRADS 1–3 on MRI as for men with PIRADS 4–5, but neither PI-RADS score nor tumor stage on MRI were found to be significant predictors in unadjusted or adjusted models (Table 2).

For patients with PIRADS 4–5, the probability of upgrading was high over the entire PSA density range ($p = 0.061$), whereas for patients with PI-RADS 1–3 the probability increased from very low for men with low PSA density to higher for those with higher PSA density ($p = 0.036$, Figure 2).

DISCUSSION

The aim of this study was to identify predictors of upgrading at prostatectomy in men with GG 1 on biopsy and pretreatment bpMRI. About half of the cancers in our study were upgraded at prostatectomy, which is consistent with previous publications [6, 7], and in our cohort, we found that PSA density was the only significant predictor for upgrading. According to exploratory analyses, however, the probability of upgrading was independent of PSA density level for patients with PI-RADS 4–5, whereas for men with PI-RADS 1–3 the probability for upgrading increased from low to high with increasing PSA density.

Our findings indicate that PSA density is of clinical importance mainly for men with PI-RADS 1–3, not for those with PI-RADS 4–5. To the best of our knowledge, this has not been previously reported. The finding is, however, supported by previous studies using multiparametric MRI, showing that the pre-diagnostic probability of GG 2–5 cancer in men with PI-RADS 1–3 lesions is strongly associated with PSA density. The risk of detecting a GG 2–5 in men with PI-RADS 1–3 and PSA density under 0.15 ng/ml/cm^3 is much lower than in those with higher PSA density; so low that a biopsy usually is not considered necessary [4, 18].

Our results suggest that men with GG 1 and PI-RADS 4–5 on bpMRI, as well as those with PI-RADS score 1–3 and a high PSA density should be recommended repeated targeted biopsies before they consider active surveillance or upfront radical treatment.

That PSA density predicts upgrading is also in line with previously published studies. In a population-based study including 4500 men, age, PSA, PSA density above 0.15 ng/ml/cm^3, clinical stage T3 and more than 4 mm cancer length on biopsy were associated with upgrading and/or upstaging in men with GG 1 cancer who underwent prostatectomy [5]. Another study concluded that PSA density better predicts upgrading after prostatectomy in men with GG 1 than PSA alone [19].

In our main regression analyses, neither the PI-RADS score nor the MRI tumor stage was significantly associated with upgrading, but the confidence intervals were wide so we cannot exclude that a clinically important association exists. Two other studies have reported an association between PI-RADS score on

multiparametric MRI and upgrading after prostatectomy in men with GG 1 on biopsy [17, 20] and considering the strong association between PI-RADS and GG in the diagnostic setting it is reasonable to assume that there is a clinically significant association also for men with a biopsy GG 1 cancer. In a recent meta-analysis including men under active surveillance, PI-RADS score was shown to predict upgrading [21]. We could not reproduce these results, and a possible explanation is the small sample size.

Limitations of our study include the small sample size and the unknown selection process leading to surgery. The latter means that our results are not representative for all patients diagnosed with GG 1, as the patients in our study might have been recommended surgery because of MRI findings, a high PSA density or rising PSA values. This limitation is shared with all similar studies. Due to this selection process, there were only 27 patients with PI-RADS score 1–3 on our sample, hence our findings need to be confirmed in larger study populations. The small sample size also necessitated selecting a few variables in the analysis and our study did not include all possible predictors for upgrading. The omission of for instance circulating testosterone levels, which was not registered in our database, limits our results [22]. Moreover, inter-rater discrepancy for MRI reading may affect the external validity of our results [23]. However, as prostate bpMRI is routinely done before biopsy at the study centre (more than 800 procedures per year) and they are read by specially trained radiologists, all radiologists involved in our study had considerable experience. Staging was accomplished by a dedicated uroradiologist with several years' experience, but staging with bpMRI has generally been reported to have poor sensitivity for identifying pT3a tumors [24]. Another limitation is how the biopsies were taken. This register-based study has recruited patients over several years and the routine for how biopsies are taken has changed over time. Hence, some patients had systematic biopsies, while others are diagnosed on targeted biopsies. Furthermore, the histological specimens were not reviewed. The limitations mentioned above are a consequence of the study design.

CONCLUSIONS

PSA density is a strong predictor for upgrading at radical prostatectomy in men with GG 1 prostate cancer on biopsy only for those with a biparametric MRI categorised as PI-RADS 1–3. For men with PI-RADS 4–5 tumor, the probability of upgrading is high regardless of PSA density. Due to this high probability of upgrading, men with GG 1 and PI-RADS 4–5 on bpMRI, as well as those with PI-RADS score 1–3 and a high PSA density, should be advised to repeated biopsies before being accepted for active surveillance.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. European Association of Urology (EAU). Prostate Cancer 2017 [Available from: http://uroweb.org/guideline/prostate-cancer/
2. Athanazio D, Gotto G, Shea-Budgell M, Yilmaz A, Trpkov K. Global Gleason grade groups in prostate cancer: concordance of biopsy and radical prostatectomy grades and predictors of upgrade and downgrade. Histopathology. 2017; 70: 1098-1106.
3. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016; 40: 244-252.
4. Norris JM, Carmona Echeverria LM, et al. What Type of Prostate Cancer Is Systematically Overlooked by Multiparametric Magnetic Resonance Imaging? An Analysis from the PROMIS Cohort. Eur Urol. 2020; 78: 163-170.
5. Vellekoop A, Loeb S, Folkvaljon Y, Stattin P. Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. J Urol. 2014; 191: 350-357.
6. Verep S, Erdem S, Ozluk Y, Kilicaslan I, Sanli O, Ozcan F. The pathological upgrading after radical prostatectomy in low-risk prostate cancer patients who are eligible for active surveillance: How safe is it to depend on bioptic pathology? Prostate. 2019; 79: 1523-1529.
7. Kaye DR, Qi J, Morgan TM, et al. Pathological upgrading at radical prostatectomy for patients with Grade Group 1 prostate cancer: implications of confirmatory testing for patients considering active surveillance. BJU Int. 2019; 123: 846-853.
8. Magheli A, Hinz S, Hege C, et al. Prostate specific antigen density to predict prostate cancer upgrading in a contemporary radical prostatectomy series: a single center experience. J Urol. 2010; 183: 126-131.
9. Boesen L, Norgaard N, Logager V, et al. Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men: The Biparametric MRI for Detection of Prostate Cancer (BIDOC) Study. JAMA Netw Open. 2018; 1: e180219.
10. Boesen L. Multiparametric MRI in detection and staging of prostate cancer. Dan Med J. 2017; 64: B5327.
11. Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol. 2013; 23: 2019-2029.

12. Kizilay F, Celik S, Sozen S, et al. Correlation of Prostate-Imaging Reporting and Data Scoring System scoring on multiparametric prostate magnetic resonance imaging with histopathological factors in radical prostatectomy material in Turkish prostate cancer patients: a multicenter study of the Urooncology Association. Prostate Int. 2020; 8: 10-15.

13. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging-Reporting and Data System: 2015, Version 2. Eur Urol. 2016; 69: 16-40.

14. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol. 2019; 76: 340-351.

15. Boesen L, Norgaard N, Logager V, et al. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7-10 Prostate Cancer in Biopsy-naive Men. Eur Urol Oncol. 2019; 2: 311-319.

16. Tamada T, Kido A, Yamamoto A, et al. Comparison of Biparametric and Multiparametric MRI for Clinically Significant Prostate Cancer Detection With PI-RADS Version 2.1. J Magn Reson Imaging. 2021; 53: 283-291.

17. Nyk Ł, Tayara O, Ząbkowski T, Kryst P, Andrychowicz A, Malewski W. The role of mpMRI in qualification of patients with ISUP 1 prostate cancer on biopsy to radical prostatectomy. BMC Urol. 2021; 21: 82.

18. Distler FA, Radtke JP, Bonekamp D, et al. The Value of PSA Density in Combination with PI-RADS™ for the Accuracy of Prostate Cancer Prediction. J Urol. 2017; 198: 575-582.

19. Oh JJ, Hong SK, Lee JK, et al. Prostate-specific antigen vs prostate-specific antigen density as a predictor of upgrading in men diagnosed with Gleason 6 prostate cancer by contemporary multicore prostate biopsy. BJU Int. 2012; 110: E494-E499.

20. Song W, Bang SH, Jeon HG, et al. Role of PI-RADS Version 2 for Prediction of Upgrading in Biopsy-Proven Prostate Cancer With Gleason Score 6. Clin Genitourin Cancer. 2018; 16: 281-287.

21. Cantiello F, Russo GI, Kaufmann S, et al. Role of multiparametric magnetic resonance imaging for patients under active surveillance for prostate cancer: a systematic review with diagnostic meta-analysis. Prostate Cancer Prostatic Dis. 2019; 22: 206-220.

22. Ferro M, Lucarelli G, de Cobelli O, et al. Circulating preoperative testosterone level predicts unfavourable disease at radical prostatectomy in men with International Society of Urological Pathology Grade Group 1 prostate cancer diagnosed with systematic biopsies. World J Urol. 2021; 39: 1861-1867.

23. Girometti R, Giannarini G, Greco F, et al. Interreader agreement of PI-RADS v. 2 in assessing prostate cancer with multiparametric MRI: A study using whole-mount histology as the standard of reference. J Magn Reson Imaging. 2019; 49: 546-555.

24. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol. 2016; 70: 233-245. ■