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Prostate Cancer

Prospective Assessment of Prostate Cancer Aggressiveness Using 3-T Diffusion-Weighted Magnetic Resonance Imaging–Guided Biopsies Versus a Systematic 10-Core Transrectal Ultrasound Prostate Biopsy Cohort

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Abstract

Background: Accurate pretreatment assessment of prostate cancer (PCa) aggressiveness is important in decision making. Gleason grade is a critical predictor of the aggressiveness of PCa. Transrectal ultrasound–guided biopsies (TRUSBxs) show substantial undergrading of Gleason grades found after radical prostatectomy (RP). Diffusion-weighted magnetic resonance imaging (MRI) has been shown to be a biomarker of tumour aggressiveness.
Objective: To improve pretreatment assessment of PCa aggressiveness, this study prospectively evaluated MRI-guided prostate biopsies (MR-GBs) of abnormalities determined on diffusion-weighted imaging (DWI) apparent diffusion coefficient (ADC) maps. The results were compared with a 10-core TRUSBx cohort. RP findings served as the gold standard.
Design, setting, and participants: A 10-core TRUSBx (n = 64) or MR-GB (n = 34) was used for PCa diagnosis before RP in 98 patients.
Measurements: Using multiparametric 3-T MRI: T2-weighted, dynamic contrast-enhanced imaging, and DWI were performed to identify tumour-suspicious regions in patients with a negative TRUSBx. The regions with the highest restriction on ADC maps within the suspicions regions were used to direct MR-GB. A 10-core TRUSBx was used in a matched cohort. Following RP, the highest Gleason grades (HGGs) in biopsies and RP specimens were identified. Biopsy and RP Gleason grade results were evaluated using chi-square analysis.
Results and limitations: No significant differences on RP were observed for proportions of patients having a HGG of 3 (35% vs 28%; p = 0.50), 4 (32% vs 41%; p = 0.51), and 5 (32% vs 31%; p = 0.61) for the MR-GB and TRUSBx cohort, respectively. MR-GB showed an exact performance with RP for overall HGG: 88% (30 of 34); for TRUS-GB it was 55% (35 of 64; p = 0.001). In the MR-GB cohort, an exact performance with HGG 3 was 100% (12 of 12); for HGG 4, 91% (10 of 11); and for HGG 5, 73% (8 of 11). The corresponding performance rates for TRUSBx were 94% (17 of 18; p = 0.41), 46% (12 of 26; p = 0.02), and 30% (6 of 20; p = 0.01), respectively.
Conclusions: This study shows prospectively that DWI-directed MR-GBs significantly improve pretreatment risk stratification by obtaining biopsies that are representative of true Gleason grade.

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1. Introduction

The Gleason grading system is the key method to describe the pathologic characteristics of prostate cancer (PCa). Of all the clinically determinable parameters, the Gleason score (GS) has proven to be the most important in measuring aggressiveness, disease outcome, and the risk of mortality from PCa [1].

Transrectal ultrasound–guided biopsy (TRUSBx) is currently the most accepted method for establishing a definite diagnosis of PCa in patients with a clinical suspicion based on prostate-specific antigen (PSA) values or digital rectal examination (DRE). The most frequently used schemes include sampling 10–12 cores with emphasis on the lateral peripheral zone and transition zone [2,3]. The tumour biopsy cores are scored according to the Gleason grading scheme to determine aggressiveness.

PCa can be multifocal and heterogeneous in composition, often presenting with well-, moderately, and poorly differentiated components in the same tumour. TRUSBx-determined GS has been shown [4–6] to be substantially discordant (undergrading in 34–38%) with the GS determined in radical prostatectomy (RP) specimens. Because risk stratification affects individualised treatment decisions and prognosis, the accurate pretreatment prediction of GS remains essential.

Multiparametric MR imaging (MP-MRI), including T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MR imaging (DCE-MRI), have all been shown (especially in combination) to localise PCa accurately [7,8]. Improved localisation of suspicious regions on MP-MRI have also been biopsy targeted under MR guidance and shown to increase tumour detection rates substantially [9,10]. DWI has been shown to provide information about tumour aggressiveness [11,12].

The aim of this study was to determine prospectively whether DWI-guided prostate biopsies could improve the pretreatment assessment of PCa aggressiveness. These results were compared with a standard clinical cohort of patients who underwent 10-core TRUSBxs. In both cohorts the performance of Gleason grades in biopsy and RP (the gold standard) was determined.

2. Materials and methods

2.1. Patients

Between August 2006 and April 2009, 123 consecutive patients underwent RP at the Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, and were retrospectively included after a PCa diagnosis was made with 10-core TRUSBx or MR-GB. Patients with prior hormonal/radiotherapy were excluded.

2.2. Transrectal ultrasound–guided biopsy sampling

Extended systematic 10-core TRUSBxs (6 lateral and 4 transition zone) were obtained using a Pro Focus B-K ultrasound device (B-K Medical, Herlev, Denmark) and 18G needles with a 17-mm sampling length. Indications for biopsies were based on clinical parameters: elevated PSA $\geq$4 ng/ml and/or abnormal DRE. TRUSBx represented the first biopsy session in these patients.

2.3. Magnetic resonance imaging

MP-MRI at 3-T (Trio Tim, Siemens, Erlangen, Germany) that included T2-weighted, DWI, and DCE-MRI was performed in patients with at least one prior negative 10-core TRUSBx but persistent clinical suspicion for PCa defined by elevating or persistently elevated PSA >4 ng/ml. Table 1 lists the MRI parameters. Apparent diffusion coefficient (ADC) maps were calculated from the DWI by the scanner. Two radiologists determined up to three tumour-suspicious regions (TSRs) per patient in consensus using the combined information of the features suspicious for malignancy on the different MP-MRI modalities. PSA values were available to radiologists. Each of the imaging modalities was scored on a tumour probability scale of 1–5 with a maximum cumulative score of 15. Per modality, the scale is defined as follows: 1, definitely no tumour; 2, probably no tumour; 3, possibly tumour; 4, probably tumour; and 5, definitely tumour. A score $\geq$8 of 15 was an indication for biopsy of a TSR.

2.4. Magnetic resonance imaging–guided biopsy

An average of 4 wk (range: 2–6 wk) following tumour detection by MP-MRI, an MR-GB (using MR-compatible 18G needles with a sampling length of 17 mm) of the previously determined TSRs was performed using a commercially available transrectal MR biopsy device (Invivo, Schwerin, Germany). The translation of initial MR imaging findings to the subsequent MR-GB was previously described in detail [13]. The lowest signal areas on the ADC maps within the TSR were used to target biopsies.

Table 1 – Magnetic resonance imaging sequence parameters

	Sequence type	Slice thickness, mm	No. of slices	In-plane resolution, mm	TR, ms	TE, ms	Averages	GRAPPA	b-values
T2-w axial	TSE	4	15–19	0.6 × 0.6	3540	104	2	–	–
T2-w coronal	TSE	4	15–19	0.6 × 0.6	3350	105	2	–	–
T2-w sagittal	TSE	4	15–19	0.6 × 0.6	3810	105	2	–	–
DWI	SE-EPI	4	15–19	2.0 × 2.0	2800	81	10	2	0, 50, 500, 800 mm^2/s
T1-w DCE	GRE (FLASH 3D)	4	14	1.8 × 1.8	37	1.47	1	–	–

TR = repetition time; TE = echo time; GRAPPA = parallel imaging factor; T2-w = T2-weighted; TSE = turbo spin echo; DWI = diffusion-weighted imaging; SE-EPI = spin echo-echo planar imaging; T1-w = T1-weighted; DCE = dynamic contrast enhanced imaging; GRE = gradient echo imaging; FLASH = fast low-angle shot imaging.

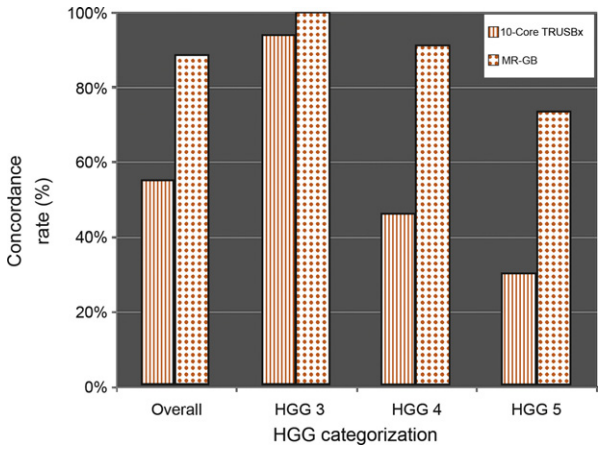

Fig. 1 – Performance rates according to highest Gleason grade (HGG) categorization: 10-core transrectal ultrasound-guided biopsy (TRUSBx) versus magnetic resonance imaging–guided biopsy (MR-GB).

2.5. Histopathologic analysis of biopsy specimens

Biopsy tissue cores were fixed in 10% neutral-buffered formalin stained with haematoxylin-eosin, and a 5-μm tissue section was prepared before evaluation by one urogenital pathologist (CAHK) with 17 yr of experience in prostate pathology. All clinical features were available to the histopathologist. For cores containing cancer, a GS was determined using the 2005 International Society of Urogenital Pathology (ISUP) criteria. The primary, secondary, and tertiary Gleason grades were determined, and the highest Gleason grade (HGG) was identified.

2.6. Reconstructed whole-mount step-section preparation

Following RP, specimens were processed and cut into 4-mm-thick slices, perpendicular to the dorsal-rectal surface and parallel to the transverse T2-weighted imaging plane. All slices were completely evaluated on 5-μm sections stained with haematoxylin-eosin. The presence and extent of PCa was outlined by the same pathologist (who also evaluated all biopsies). Each tumour was graded according to the 2005 ISUP modified Gleason grading system [14]. As with the assessment of biopsies, the primary to tertiary Gleason grades and the HGG identified within the prostate was noted.

2.7. Statistical analysis

Cross-tabulation analysis of the biopsy and RP findings was done. For both MR-GB and TRUSBx cohorts, performance rates (percentage) with RP were determined for the HGG. Then, for RP HGG 5, undergrading was further defined as "substantial" if the corresponding biopsy was HGG 3. Finally, performance rates between biopsy and RP HGG groups were determined separately for patients with PSA $\leq$10 ng/ml and those with PSA $>$10 ng/ml. Chi-square analyses with Fisher exact tests were performed to evaluate the significance of differences between MR-GB and TRUSBx performance rates. The *t* test was performed to determine the differences in mean PSA, prostate volume, and dominant tumour volume. Significance was considered when $p < 0.05$. Statistical analyses were performed with SPSS software v.16.0.01 (IBM Corp, Somers, NY, USA) (Figs. 1–3).

3. Results

Ninety-eight patients fulfilled the inclusion criteria. In 34 of 98 patients a tumour diagnosis was made using MR-GB (median: 3 cores, range: 1–5; median number of biopsies/TSR: 2, range: 1–3), and in 64 of 98 patients a diagnosis was made using 10-core TRUSBx. The median duration of the

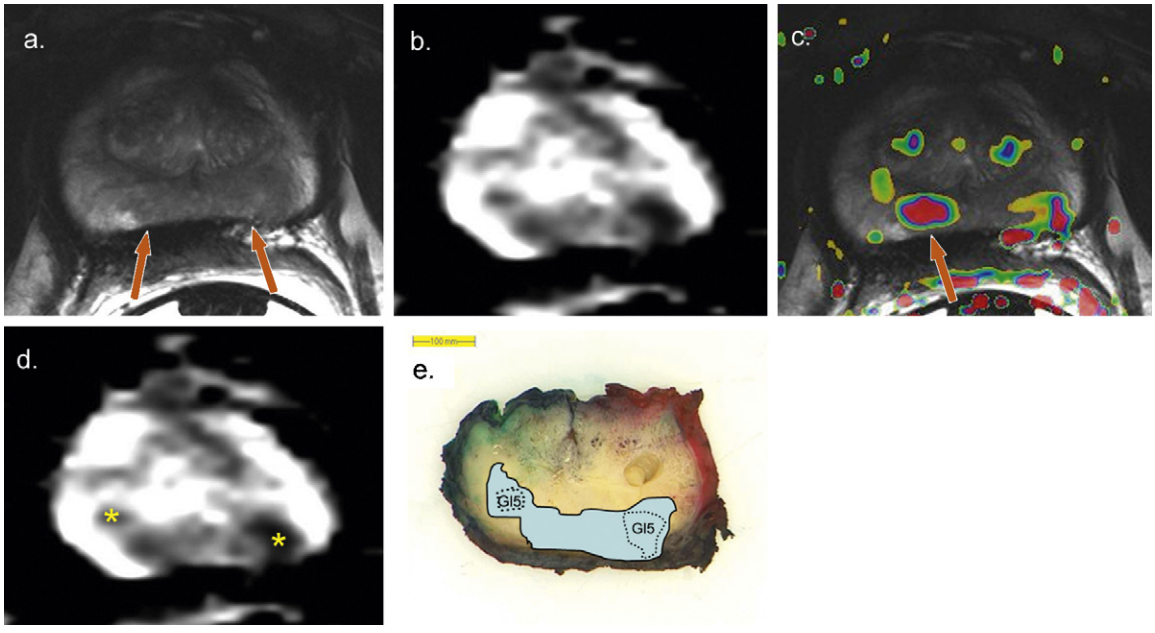

Fig. 2 – Patient with prostate-specific antigen of 11 ng/ml. Transrectal ultrasound–guided biopsy revealed a Gleason 3 plus 4 score. (a) T-2 weighted image shows a large tumour region in the entire dorsal peripheral zone (arrows). (b) On the apparent diffusion coefficient (ADC) maps, restriction is clearly visible for the same lesion. (c) On dynamic contrast-enhanced imaging, the Ktrans map shows irregular enhancement of the tumour. (d) Within the restricted regions, however, two regions with higher restriction are visible (yellow asterisks). (e) On the corresponding pathology step section, the tumour is delineated in light blue, corresponding to the findings on magnetic resonance imaging. Regions with focal Gleason grade 5, delineated with a dotted line, correspond exactly to the ADC "hot spots" findings. Final pathology showed a Gleason 3 + 4 + 5, pT3 tumour.

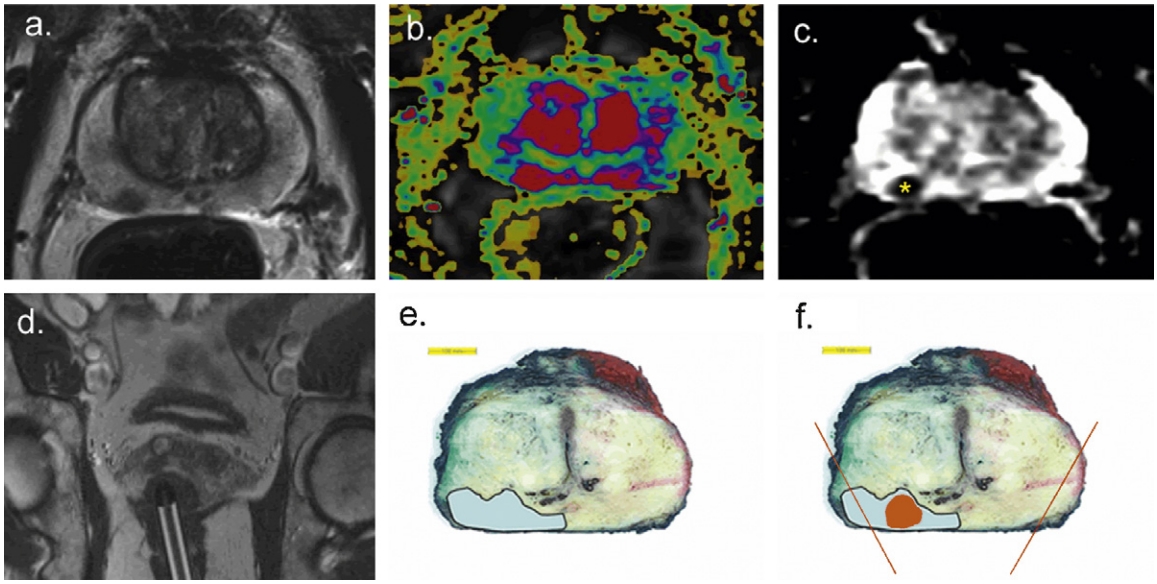

Fig. 3 – Patient with prostate-specific antigen of 12 ng/ml and a four times prior negative transrectal ultrasound–guided biopsy. (a) T2-weighted image with focal lesion visible in right peripheral zone. (b) On the dynamic contrast-enhanced imaging Ktrans map, diffuse enhancement of the peripheral zone is seen. (c) Apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging shows a focal small lesion with clear restriction (yellow asterisk). (d) True fast imaging with steady-state precession image during biopsy with the needle guider directed towards the most suspicious region before taking a magnetic resonance imaging–guided biopsy (MR-GB). The MR-GB revealed a Gleason 4 component. (e) Prostatectomy step section showed a pT2c tumor in the right peripheral zone (light blue = Gleason 3 component; red = Gleason 4). (f) The volume of the Gleason 3 component is underestimated by the MRI; however, volume of the focal "hot spot" on the ADC images exactly matches with the final pathology: Gleason 4. The red lines indicate the lateral areas where TRUSBx usually sample the prostate and why this can miss the hotspot of aggressive tumour.

procedure for MR-GB was 29 min (range: 15–75 min). The median duration between MR-GB and RP was 6 wk (range: 3–11 wk) and between TRUSBx and RP was 5 wk (range: 2–9 wk). Table 2 summarises the patients' demographic and clinical parameters. No significant differences between MR-GB and TRUSBx cohorts were observed for percentage stage pT3 (35% vs 38%; $p = 0.83$), mean dominant aggressive tumour volume (4.85 cm^3 vs 4.52 cm^3; $p = 0.69$), or mean prostate volume (41 cm^3 vs 36 cm^3; $p = 0.61$). No significant differences were observed for the overall proportions of patients on RP having HGG 3 (35% vs 28%; $p = 0.50$), 4 (32% vs 41%; $p = 0.51$), and 5 (32% vs 31%; $p = 1.00$) for the MR-GB and TRUSBx cohort, respectively. The RP presence of HGG 4 was associated with extracapsular extension in 39–46% and the presence of HGG 5, in 64–70%.

Table 3 and 4 present a summary of biopsy and RP findings. Categorisation of HGG on biopsy and RP revealed an overall performance for MR-GB of 88% (30 of 34) versus 55% (35 of 64) for TRUSBx. In the MR-GB cohort, an exact performance with RP HGG 3 was 100% (12 of 12); for HGG 4, 91% (10 of 11); and for HGG 5, 73% (8 of 11). The corresponding performance rates for TRUSBx were 94% (17 of 18; $p = 0.41$), 46% (12 of 26; $p = 0.01$), and 30% (6 of 20; $p = 0.02$), respectively (Fig. 1). For biopsies determined as low grade (HGG 3), the positive predictive value (PPV) for MR-GB to represent true low grade was 92% (12 of 13); for TRUSBx the PPV was 45% (17 of 38; $p = 0.001$). Overall, undergrading of tumours with RP HGG 4/5 was 46% (25 of 46) for TRUSBx and 5% (1 of 22) for MR-GB.

No overgrading was observed for MR-GB, although this was evident in one TRUSBx patient (false HGG 4 instead of 3). Undergrading for RP HGG 5 was 27% (3 of 11) in MR-GB compared with 70% (14 of 20) for TRUSBx. TRUSBx showed substantial undergrading (RP HGG 5) in 57% (8 of 14), whereas no substantial undergrading occurred with MR-GB.

Table 2 – Patient and pathology characteristics

	MR-GB	10-core biopsy	Significance (p value)
No. of patients	34	64	NA
Age, yr (range)	66 (51–74)	66 (41–74)	0.22
No. of biopsies (range)	3 (1–5)	10	NA
Stage (%)			
pT2	22/34 (65)	40/64 (62)	0.83
pT3	12/34 (35)	24/64 (38)	
Prostate volume			
Median, cm^3 (range)	41 (12–79)	36 (17–126)	0.61
PSA			
Median, ng/ml (range)	12 (3–40)	8 (2–47)	0.02*
DA tumour volume			
Median, cm^3 (range)	4.85 (0.1–33)	4.52 (0.1–33.5)	0.69
Prevalence of tumours in RP			
HGG category, %			
HGG 3	35 (12/34)	28 (18/64)	0.50
• Stage pT3	0 (0/12)	0 (0/18)	NA
HGG 4	32 (11/34)	41 (26/64)	0.51
• Stage pT3	45 (5/11)	38 (10/26)	0.73
HGG 5	32 (11/34)	31 (20/64)	1.00
• Stage pT3	64 (7/11)	80 (16/20)	0.41

MR-GB = magnetic resonance imaging guided prostate biopsies; NA = not applicable; PSA = prostate-specific antigen; DA = dominant aggressive; RP = radical prostatectomy; HGG = highest Gleason grades.

Table 3 – Cross-tabulations for cohorts based on highest Gleason grade grouping

		Prostatectomy			
		HGG 3	HGG 4	HGG 5	
TRUSBx	HGG 3	17	14	8	44% (17/39)
	HGG 4	1	12	6	63% (12/19)
	HGG 5	0	0	6	100% (6/6)
		94% (17/18)	46% (12/26)	73% (8/11)	55% (35/64)
MR-GB	HGG 3	12	1	0	92% (12/13)
	HGG 4	0	10	3	77% (10/13)
	HGG 5	0	0	8	100% (8/8)
		100% (12/12)	91% (10/11)	73% (8/11)	88% (30/34)

HGG = highest Gleason grade; TRUSBx = transrectal ultrasound-guided biopsy; MR-GB = magnetic resonance imaging guided biopsy.

Table 4 – Performance analysis between biopsy and radical prostatectomy cohorts

	Performance rates MR-GB, %	Performance rates 10-core TRUSBx, %	Significance (p value)
Overall Bx concord. with RP HGG	88 (30/34)	55 (35/64)	0.001*
Bx concord. with RP HGG 3	100 (12/12)	94 (17/18)	0.41
Bx concord. with RP HGG 4	91 (10/11)	46 (12/26)	0.01*
Bx concord. with RP HGG 5	73 (8/11)	30 (6/20)	0.02*
Bx concord. with RP HGG 4/5	95 (21/22)	54 (25/46)	0.001*
PPV for Bx and RP HGG 3	92 (12/13)	45 (17/38)	0.003*
PSA			
≤10 ng/ml (percentage of patients)	35 (12/34)	69 (44/64)	0.01*
Overall HGG performance	100 (12/12)	59 (26/44)	0.01*
>10 ng/ml (percentage of patients)	65 (22/34)	31 (20/64)	0.01*
Overall HGG performance	82 (18/22)	45 (9/20)	0.01*

MR-GB = magnetic resonance imaging guided biopsy; TRUSBx = transrectal ultrasound-guided biopsy; RP = radical prostatectomy; Bx = biopsy; concord. = concordance; PPV = positive predictive value; PSA = prostate-specific antigen.
* Denotes significance.

PSA values for the MR-GB cohort (median PSA: 12 ng/ml) and TRUSBx cohort (median PSA: 8 ng/ml) showed a significant difference ($p = 0.02$). Subgroup analysis was performed for patients with PSA >10 ng/ml versus PSA ≤10 ng/ml. For patients with PSA ≤10 ng/ml, 0% (0 of 12) undergrading was seen for MR-GB, whereas for TRUSBx, undergrading occurred in 41% (18 of 44; $p = 0.01$). For patients with PSA >10 ng/ml, MR-GB revealed an 18% (4 of 22) undergrading and TRUSBx a 55% (11 of 20; $p = 0.01$) undergrading. Table 3 summarises the performance rates. Figs. 2 and 3 show imaging findings in a TRUSBx and MR-GB patient.

4. Discussion

In this prospective study, 3-T DWI targeted MR-GB sampling improved the pretreatment assessment of PCa aggressiveness. The Gleason grades as determined with MR-GB showed a high performance rate (88%) with prostatectomy. This is in sharp contrast to 10-core TRUSBx, which showed a 55% performance rate. In this study the most abnormal ADC regions following MP-MRI localisation of tumour were used to target biopsies. To our knowledge, this is the first prospective report on the use of DWI to obtain PCa biopsies that are more representative for true RP Gleason grade. These results confirm prior retrospective studies on the ability of DWI to visualise tumour aggressiveness and serve as a platform for improved pretreatment prediction of true Gleason grades [15,16].

The importance of correct pretreatment assessment of PCa aggressiveness is widely accepted. A shift from radical therapy to individualised tailored therapy has been advocated [17]. A cornerstone of this individual-based risk stratification is the correct pretreatment identification of true Gleason grades. Patients without grade 4/5 components are potential candidates for less invasive treatment, such as active surveillance or local therapy [18]. Patients harbouring high-grade components definitely need further evaluation for possible extracapsular extension and skeletal or nodal metastasis. High-grade PCa managed with noncurative intent substantially reduces life expectancy [19]. A European Organisation for Research and Treatment of Cancer trial showed that high-risk patients definitely benefit from adjuvant hormone therapy. Correctly stratifying patients into low or high risk, therefore, is of utmost importance [20].

Numerous studies have addressed the correlation between GS in biopsy and corresponding RP. These show that increasing the number of biopsies increases the performance. In earlier studies using sextant biopsies, undergrading was reported in 44–60% [21,22], whereas recent studies with extended biopsy schemes reported lower values of 32–38% [4,5,21,23]. When comparing overall

performance rates between studies, the most important factor that needs diligent consideration is the prevalence of low-grade tumours. Using extended 12 cores, San Francisco et al. [24] showed an exact GS performance rate of 76%. However, the prevalence of low-grade tumours in their RP was 72%. This artificially increases the overall performance rates. When only evaluating their high-grade tumours (HGG 4/5), a 32% undergrading was still evident. A large cohort from John Hopkins [25] revealed an overall GS agreement of 76%. The prevalence of low-grade tumours in RP was high at 67%. When only the high-grade tumours on RP were chosen, an undergrading of 42% was noted. Our TRUSBx revealed a 46% undergrading of tumours identified as HGG 4/5 on RP. This is in agreement with these two studies. Yet, for MR-GB, only a 5% undergrading of high-grade tumours was seen. Our TRUSBx revealed substantial undergrading in 57% of RP HGG 5 tumours (ie, showing a biopsy HGG of 3). In all cases of HGG 5 undergrading, MR biopsies revealed a HGG of 4, thus showing a more acceptable underestimate. The prevalence of HGG 3, 4, and 5 groups in our two cohorts did not show statistically significant differences. We therefore believe our results with MR-GB show a substantial improvement of performance rates compared with current practice and literature. In addition, with MR-GB, only a median of 3 cores per patient were taken, instead of 10 with TRUSBx.

Clinically important factors may be associated with prostate biopsy undergrading. Isariyawongse et al. [26] showed that both age and PSA values are important in this respect. Biopsies in patients with PSA values 10–20 ng/ml and PSA >20 ng/ml had odds ratios of 2.11 and 3.64, respectively, compared with PSA <10 ng/ml for representing undergrading of true GS in prostatectomy. Our overall baseline PSA values for the two cohorts did indeed show a significant difference, however, to the detriment of MR-GB where higher PSA values were found. Usually a PSA cut-off value of 10 ng/ml is used as an integral part of decision making regarding further diagnostic tests and treatment (ie, opting for active surveillance) [27]. We therefore performed a subgroup analysis for patients with PSA ≤10 ng/ml and those with PSA >10 ng/ml. For both subgroups, MR-GBs were superior in performance rates. The PSA value evidently did not influence the performance rates of biopsies with RP findings in our study. Stackhouse et al. [28] evaluated additional factors that may predict undergrading. Of relevance to our study would also be their identified factors: patient age and prostate weight (and thus prostate volume). Increasing age has been shown to have increasing odds ratios for undergrading. In our cohort, both groups had the same median ages of 66 yr ($p = 0.22$). No significant differences in prostate volumes ($p = 0.61$) or dominant tumour volume ($p = 0.69$) were seen in our cohorts.

In addition, we evaluated two further factors that in our opinion may also represent biases in cohorts and possibly having an influence on the degree of undergrading: dominant aggressive tumour volume and tumour stage at RP. In a paper by Resnick et al. [29] with a large cohort of 2411 patients, biopsy and prostatectomy features of patients at first, second, and third TRUSBx sessions were evaluated. With each increase in the number of biopsy sessions, the undergrading of GS ≥7 increased from 18% at the first biopsy session, to 55% at the second, to 58% at the third, despite the increasing overall prevalence of GS 6 tumours with every subsequent session. These findings would suggest an increased likelihood of undergrading for our repeat biopsies. On the contrary, however, despite representing a rebiopsy session, our MR-GB still outperformed a first-session 10-core TRUSBx. We therefore believe that despite these minor differences between our cohorts, no important clinical or pathologic factor could be determined that might bias our MR-GB cohort to a more favourable group regarding the likelihood of undergrading.

DWI is rapidly gaining importance as a valuable noninvasive biomarker for determining tumour response to therapy in a large variety of tumours [30]. In addition, DWI is also increasingly being used to determine tumour aggressiveness noninvasively. Its role for the assessment of aggressiveness and cellularity in breast tumours [31], soft tissue sarcomas [32], renal tumours [33], and hepatocellular tumours [34] has been reported. For PCa, recent data have shown that ADC values derived from DWI have a high discriminatory performance in separating low-grade versus combined intermediate- and high-grade cancers [15].

A number of limitations exist. A randomised trial between MR-GB versus TRUSBx or performing both TRUS- and MR-guided biopsies in the same patient would represent the ideal scenario. Our approach, however, was to determine the performance in a routine clinical setup as performed in our hospital. A second limitation was the relatively low number of patients. Nonetheless, differences were statistically significant, even with this small number of patients. Although a multiparametric approach has been proven to be the most useful for the evaluation of PCa on MR imaging, it still requires a high level of expertise, and observer variability may be an issue [35]. Our results represent findings of an expert centre that uses in-house developed analytical software and whose clinicians have numerous years of experience, so they might be an overoptimistic prediction of performance attainable in smaller nonexpert institutions. A final limitation is the potential differences of the two cohorts as discussed previously.

5. Conclusions

Biopsies targeted towards the most abnormal regions on 3-T DWI MR imaging represent a substantially improved method for the assessment of true tumour aggressiveness and can therefore represent an indispensable tool in the diagnosis and management of patients with PCa. This will probably also hold true for other malignancies. Thus its use is strongly advocated.

***Author contributions*:** Thomas Hambrock 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: Hambrock, Hoeks, Huisman, Barentsz
Acquisition of data: Hambrock, Hoeks, Bouwense, Hulsbergen-van de Kaa.
Analysis and interpretation of data: Hambrock, Schröder, Scheenen, Huisman, Barentsz, Fütterer.

Drafting of the manuscript: Hambrock, Barentsz.
Critical revision of the manuscript for important intellectual content: van Oort, Schröder, Fütterer, Huisman.
Statistical analysis: Hambrock.
Obtaining funding: Barentsz.
Administrative, technical, or material support: Bouwense.
Supervision: Barentsz.
Other (specify): None.

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