Original Paper

Additive Value of Transrectal Systematic Ventral Biopsies in Combination with Magnet Resonance Imaging/Ultrasound Fusion-Guided Biopsy in Patients with 3 or More Negative Prostate Biopsies

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Abstract

Introduction: Patients with consistent suspicion for prostate cancer (PCa) and multiple negative prebiopsies prior to multiparametric magnetic resonance imaging (mpMRI) are still frequently evaluated for an image-guided biopsy and are reported with heterogeneous detection rates. The inclusion of a systematic biopsy (SB) is also still recommended with predominant sampling within the posterior/peripheral zone of the prostate. The aim of this study was (I) to evaluate PCa detection rates using a modified 10 core SB template including anterior biopsies in combination with mpMRI/ultrasound fusion-guided targeted biopsy (TB) in patients with 3 or more negative prebiopsies and (II) to compare mpMRI index lesion localization with histologically confirmed localization from associated prostatectomy samples. *Methods:* Overall 1,337 consecutive patients underwent sensor-based registration TB of the prostate and a subsequent 10-core SB between January 2012 and December 2015 at our institution. For this study, 101 patients with ≥3 negative prebiopsies and prostate imaging – reporting data system lesions ≥3 were pooled prospectively and underwent TB and a modified SB including 2 ventral (anterior) biopsies. Detection rates were estimated for the modified SB, TB, and its combi-

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nation. A subgroup analysis of 35 patients undergoing prostatectomy was performed by a head-to-head comparison of mpMRI index lesion and histologically confirmed PCa index lesion localization. ***Results:*** The overall detection rate for PCa was 54.5%. The combination of TB and SB detected 14 (25.4%) more cases missed by TB alone ($p < 0.001$) and 7 (12.7%) more cases missed by SB alone ($p = 0.016$), respectively. A postoperative Gleason upgrade was seen in 12/35 (34.3%) cases within the TB group and in 14/35 (40.0%) in the SB group, respectively. The subgroup analysis showed a predominant location of PCa index lesions anteriorly at the level of the midgland. The MRI detection rate of the anteriorly located index lesions was 70.4% (15/21 cases) with a clinically significant Gleason score ($\geq 3 + 4 = 7a$ [International Society of Urological Pathology grade 2]) in 80.9%. Interestingly a modified SB template detected 90.5% (19/21) of the anteriorly located index lesions. ***Conclusion:*** Our data suggest that in patients with multiple prebiopsies PCa seems to be predominantly located anteriorly. We suggest the general integration of anterior biopsies despite TB in repeat biopsy patients.

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Introduction

Implementation of multiparametric magnet resonance imaging (mpMRI) in the prostate cancer (PCa) diagnostic pathway [1] and the application of MRI/ultrasound (US) fusion targeted biopsy (TB) have resulted in increased PCa detection rates [2]. The aim of mpMRI is to identify PCa index lesions representing the largest tumor focus and also clinically significant PCa (usually associated with the highest Gleason score) by using a standardized prostate reporting system (the prostate imaging – reporting data system [PI-RADS]) [3–5]. The combination of mpMRI and TB plus a subsequent systematic biopsy (SB) has high detection rates of clinically significant PCa [6]. While mpMRI already shows high sensitivities for detecting clinically significant PCa index lesions [7], the combination of TB and subsequent SB seems to be superior in detecting significant PCa to mpMRI alone [8, 9]. Especially small nonindex lesions representing clinically significant PCa can be missed by mpMRI and TB alone [10].

However, in biopsy-naïve men, the recently published PRECISION trial showed that MRI could be used as prebiopsy risk assessment if MRI results were not suggestive of PCa [11]. Furthermore, the PROMIS study concluded in case of mpMRI as a triage test before first prostate bi-

opsy showed that MRI could identify a quarter of men who might safely avoid an unnecessary biopsy and might improve the detection of clinically significant cancer [12]. In addition, a recently published high-quality standard study showed that in biopsy-naïve men undergoing mpMRI, biopsy may be omitted in half of men, and fewer insignificant PCa are detected by only missing 4% clinical significant PCa by not performing SB [13].

But during repeat biopsy, the inclusion of a 10–12 core SB in combination with a TB is still recommended [14].

Despite the promising results of using mpMRI in PCa diagnostics, still patients with multiple prebiopsies prior to TB can be observed. Detection rates of SB at initial biopsy of 20–30% with constant decrease down to 4–12% at the time of a 4th biopsy have been reported [15, 16]. Concerning the histopathological localization of PCa in biopsy-naïve patients, it seems to be predominantly located with up to 90% within the posterior part of the prostate, whereas only 10% is located anteriorly [17, 18]. In contrast, PCa localization differs drastically in patients with prior negative biopsies, where PCa is located in the anterior part of the prostate in about 50–80% [19–21]. This is reflected by modified protocols for SB in a rebiopsy setting, such as including the anterior prostate region in the biopsy protocol and increasing the number of cores taken [22].

However, there are little data available on histological findings, especially in patients with a history of at least 3 prior negative biopsies undergoing MRI/US fusion-guided biopsy. Hence, available information during MR imaging and potential histological data postoperatively need to be analyzed for that subgroup. To our knowledge combining TB with a modified 10 core SB including a left and right ventral (anterior) instead of a left and right lateral biopsy has not been reported yet. Therefore, the aim of this study was (I) to estimate TB, SB, and combined detection rates including a modified 10 core template in patients with at least 3 negative prebiopsies and (II) to compare MR index locations with postoperatively confirmed histological data.

Methods

Patient Population
A total of 1,337 consecutive patients underwent TB of the prostate and a subsequent 10-core SB between January 2012 and December 2015 at our institution. At the time of biopsy, all enrolled patients signed a written informed consent for the intervention, data acquisition, data appraisal, and publication according to the Declaration of Helsinki and authorized by the institutional ethical review board (EA1/283/14 and EA1/012/12).
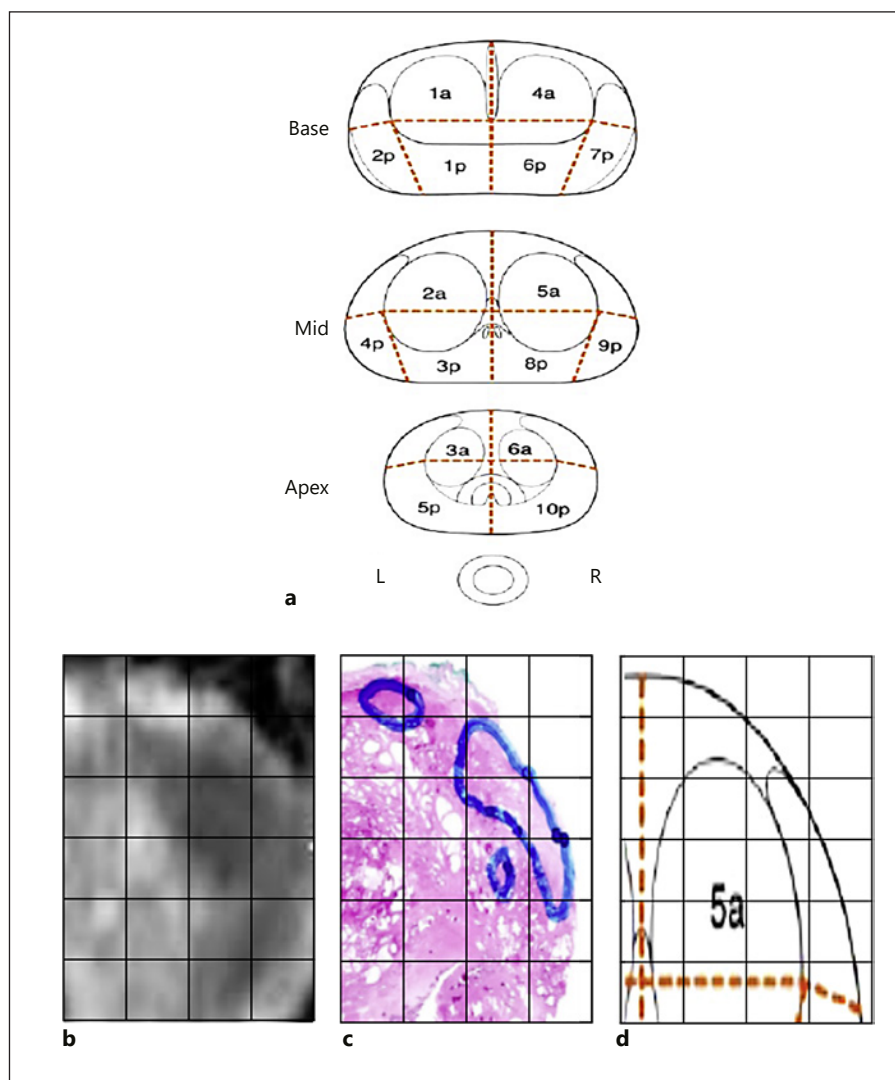
Fig. 1. Histopathological correlation of MRI prelocated index lesions location according to PI-RADS: (**a**) PI-RADS template for standardized reporting (a, anterior; p, posterior; 25); (**b**) representative DWI axial section with ADC-map of an anteriorly and centrally located index lesion within the midgland level with a 5 mm grid overlay; (**c**) example of a histopathological hematoxylin-eosin (HE) slice with marked malignant area of a matching lesion anteriorly and centrally located at the midgland level with a 5 mm grid overlay; (**d**) the representing anterior quarter within the PI-RADS template at the midglandlevel.

For the study at hand, all patients with a normal DRE and a history of at least 3 standard systematic 10–12-core transrectal ultrasound (TRUS) biopsies with no histological proof of PCa or high-grade prostatic intraepithelial neoplasia underwent a modified 10-core SB subsequent to TB including 2 ventral (anterior) biopsies. Based on these inclusion criteria, we were able to pool 108 patients prospectively. We had to exclude 3 patients based on mpMRI acquisition artefacts, 2 patients who had refused a complete SB, and 2 patients who had been operated in different hospitals and for whom insufficient postoperative histopathological data were available. Thus, 101 patients finally met study inclusion criteria.

Multiparametric Magnetic Resonance Imaging
All included patients underwent a 3 Tesla mpMRI (Magnetom Skyra, Siemens Medical Systems, Erlangen, Germany) without endorectal coil using standardized imaging protocols in accordance with current guidelines. This protocol included multiplanar (axial and coronal), high-spatial resolution T2-weighted turbo spin-echo sequences (T2w TSE), axial T1-weighted images (T1w), axial diffusion weighted images ([DWI] measured b values 0, 400, and 800 /mm^2, calculated b value of 1,000–1,400 s/mm^2) and dynamic contrast-enhanced sequences (DCE-MRI). T2-weighted imaging and DWI were performed in all patients. DCE-MRI was only performed in only 77 (76.2%) patients. The evaluation and validation of the mpMRI image data were performed or supervised by experienced uro-radiologists in compliance with the guidelines of the European Society of Urogenital Radiology according to PI-RADS version 1.0. The lesion with the highest PI-RADS score was defined as the index lesion in patients with multiple lesions and further included in the analysis. The location of the index lesion was described by 3 definitions: apical vs. mid gland vs. basal, peripheral vs. central, and ventral (anterior) vs. dorsal (posterior).

MRI Fusion-Guided and Modified SB
All included patient with a PI-RADS score of ≥3 underwent TB and subsequent SB. Prior to the biopsy, antibiotic prophylaxis with a fluoroquinolone (i.e., Ciprofloxacin) was initiated. After image fusion by sensor-based registration, a TB with a median of 2 cores

Table 1. Patient Characteristics (n = 101)

Characteristics	
Age, years	71 (51–82)
PSA, ng/mL	12.3 (1.58–39)
Prostate volume, mL	52 (12–174)
PI-RADS score	4 (3–5)
Biopsies before TB, n	3 (3–12)
Diagnosis	
PCa	55 (54.5)
BPH	14 (13.9)
Prostatitis	6 (5.9)
hgPIN	2 (1.9)
Normal tissue	24 (23.8)
Treatment of PCa (n = 55)	
oRP	21 (38.2)
RARP	14 (25.5)
AS	12 (21.8)
Radiation	7 (12.7)
Androgen deprivation therapy	1 (1.80)
cT-Stage (n = 55)	
cT1c	48 (87.3)
cT2a	5 (9.10)
cT2c	2 (3.60)
pT-Stage (n = 35)	
pT2a	3 (8.57)
pT2c	21 (60.0)
pT3a	8 (22.9)
pT3b	2 (5.70)
pT4	1 (2.83)

Values are presented as n (%) or mean ± SD. TB, target biopsy; PCa, prostate cancer; BPH, benign prostatic hyperplasia; hgPIN, high-grade intraprostatic neoplasia; oRP, open retropubic radical prostatectomy; RARP, robotic assisted radical prostatectomy; AS, active surveillance; ADT, androgen deprivation therapy; cT, clinical stage; pT, pathological tumor stage.

(range 2–4) of the prostate was performed, using the high-end US machine HiVison Preirus (Hitachi Medical Systems, Tokyo, Japan) or Aplio 500 (Toshiba [Canon Medical], Otawara, Japan) with an endocavity endfire probe (11C3, Toshiba [Canon Medical], Otawara, Japan; EUP V53 W, Hitachi medical Systems, Tokyo, Japan) or bipolar probe (EUP CC531, Hitachi, Medical Systems, Tokyo, Japan), as described previously [4]. Consecutively a modified 10 core systematic TRUS biopsy similar to a described apical anterior horn biopsy [23] without local anesthesia was performed. The template was consisting of right and left apical, right and left intermediate, right and left basal, right and left para-urethral, right and left ventral (anterior) biopsies. Concerning the right and left ventral (anterior) biopsy, the endorectal US probe was positioned in the sagittal plane, such that the needle guide was positioned anteriorly with respect to the probe. This modified template is performed in our institution since December 2012. Both TB and SB were performed by the same physicians (A.M., C.S., H.C.) in one biopsy session. All scores were plotted and documented separately.

Histopathology and Correlation of Localization

All biopsy specimens were examined and analyzed by an experienced uro-pathologist. After paraffin embedding and slicing, a hematoxylin-eosin (HE) staining was performed. A significant PCa was defined by GS ≥3 + 4 = 7 (International Society of Urological Pathology [ISUP] grade 2). The overall total Gleason score of each patient was defined as the highest Gleason score of all scores. In all cases in which a prostatectomy was performed, the prostatectomy specimens were assessed according to the pathologic assessment of radical prostatectomy specimens (TNM 2009, WHO 2004, ISUP 2005): After fixation, the specimen was dried and painted with different colors using ink to orient the gland and to clearly delineate the surgical margins. Three-millimeter wholemount sections were divided into halves (or quadrants, in a large gland) to fit into standard-size cassettes used for paraffin embedding. Standard HE stains were performed on all sections, all apical and bladder neck sections and the single embedded sections from each seminal vesicle [24]. To perform also an estimation of tumor extent within the prostate gland, PCa lesions are manually circled on the HE stains. The location of the highest Gleason score was taken as the histopathological index tumor. To improve the comparability between histopathological sections and MR images, the microscopically identified index lesion was compared to a corresponding DWI with a 5 mm grid overlay. The location was similarly described to PI-RADS as apical vs. mid gland vs. basal, peripheral vs. central, and anterior vs. posterior (Fig. 1a–d) [25].

Statistical Analysis

All statistical calculations were performed using SPSS version 20 (IBM Corp., Somers, NY, USA). Results are reported as frequencies and percentages for all categorical outcomes. McNemar test was applied to test for asymmetries in detection frequencies between SD or TB alone versus SB and TB combined. Statistical tests were two-sided unless stated otherwise and a p value <0.05 was taken to indicate statistical significance. No adjustment for multiple comparisons has been made, and all p values constitute exploratory data analysis and do not allow for confirmatory generalization of results.

Results

Descriptive data are shown in Table 1. The median age was 71 years (range 51–82 years), and the median PSA was 12.3 ng/mL (range 1.58–39 ng/mL). Out of 101 included patients, the overall PCa detection rate was 54.5%. The detected Gleason scores ranged from 3 + 3 = 6 (ISUP1) in 25 (45.5%) cases, 3 + 4 = 7a (ISUP2) in 8 (14.6%) cases, 4 + 3 = 7b (ISUP3) in 7 (12.7%) cases, 4 + 4 = 8 (ISUP 4) in 11 (20.0%) cases, and 4 + 5 = 9 (ISUP 5) in 4 (7.20%) cases.

As shown in Table 2, TB detected 41 (74.5%) PCas with the following distribution: 3 + 3 = 6 (ISUP1) in 16 (64.0%) cases, 3 + 4 = 7a (ISUP2) in 5 (62.5%) cases, 4 + 3 = 7b (ISUP3) in 7 (100%) cases, 4 + 4 = 8 (ISUP 4) in 9 (81.8%) cases, and 4 + 5 = 9 or higher (ISUP 5) in 4 cases (100%).

Table 2. Comparison of positive biopsy depending on Gleason score

Gleason score	3 + 3 = 6 (ISUP 1)	3 + 4 = 7a (ISUP 2)	4 + 3 = 7b (ISUP 3)	≥4 + 4 = 8 (≥ISUP 4)	Total	p value
SB + TB	25	8	7	15	55	–
SB	20	8	7	13	48	0.016*
TB	16	5	7	13	41	0.001*

* McNemar's test comparing SB or TB alone with the combination of SB and TB. ISUP, International Society of Urological Pathology; SB, systematic biopsy; TB, target biopsy.

Table 3. Accordance of MRI and histopathological location and biopsy distribution

	MRI index location	Histological index location	True positive: MRI matching histological location	Location of positive TB	Location of positive SB
Base	7	1	1 (100)	1	1
Midgland	23	26	20 (76.9)	19	22
Apex	5	8	5 (62.5)	7	8
Total	35	35	26 (74.2)	27	31
Posterior (dorsal)	17	14	11 (78.6)	11	13
Anterior (ventral)	18	21	15 (71.4)	16	19
Total	35	35	26 (74.3)	27	32
Peripheral	20	26	17 (65.3)	18	24
Central	15	9	6 (66.7)	9	7
Total	35	35	23 (65.7)	27	31

MRI, magnetic resonance imaging; TB, target biopsy; SB, systematic biopsy.

In contrast, 48 (87.2%) PCas have been detected by SB with the following distribution: 3 + 3 = 6 (ISUP1) in 20 (80%) cases, 3 + 4 = 7a (ISUP2) in 8 (100%) cases, 4 + 3 = 7b (ISUP3) in 7 (100%) cases, 4 + 4 = 8 (ISUP 4) in 9 (86.6%) cases, and 4 + 5 = 9 or greater (ISUP5) in 4 (100%) cases (Table 2). The combination of TB and SB detected 14 (25.4%) additional cases that were missed by TB alone ($p < 0.001$; McNemar's test) and 7 (12.7%) cases missed by SB alone ($p = 0.016$; McNemar's test). SB alone detected 7 more cases than TB alone, though did not reach statistical significance ($p = 0.189$; McNemar's test).

Thirty-five out of 55 PCa patients subsequently underwent radical prostatectomy. The postoperative Gleason score distribution was within this subgroup: 3 + 3 = 6 (ISUP1) in 4 (11%) cases, 3 + 4 = 7a (ISUP2) in 13 (37%) cases, 4 + 3 = 7b (ISUP3) in 11 (31%) cases, 4 + 4 = 8 (ISUP4) in 2 (6%) cases, and 4 + 5 = 9 or 5 + 4 = 9 (ISUP5) in 5 cases (15%). The remaining other 20 (36.3%) PCa cases underwent other treatments; displayed in Table 1.

A Gleason upgrade from biopsy results to postoperative Gleason scores was seen in 12/35 (34.3%) cases within the TB group and in 14/35 (40.0%) in the SB group, respectively.

The subgroup analysis showed based on histopathology a predominant location of the PCa index lesions anteriorly (21/35). The MRI detection rate of the anteriorly located index lesions was 70.4% (15/21 cases) with a clinically significant Gleason score (≥3 + 4 = 7a [ISUP2]) in 80.9% of the cases. The modified SB template detected 90.5% (19/21) of the anteriorly located index lesions.

A head-to-head comparison of mpMRI and histopathology locations including the distribution of Gleason scores was plotted in Figure 2a and b and also distributed in Table 3. The visual distribution of the mpMRI loca-
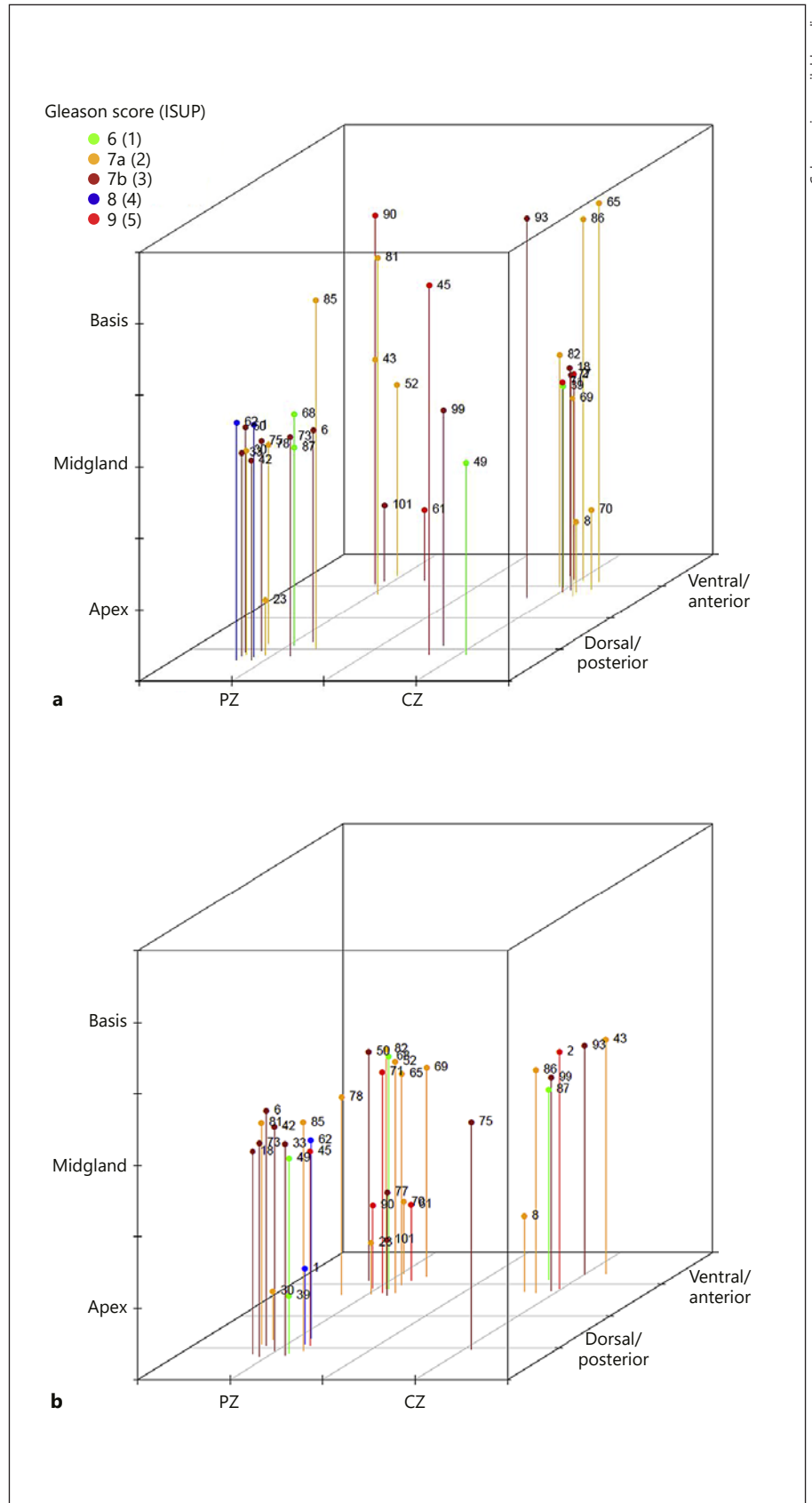
Fig. 2. 3D distribution of (**a**) MRI index-lesion location and associated Gleason score (ISUP; **b**) Histopathology index-lesion location and associated Gleason score (ISUP). Numbers represent individual patient IDs to allow for comparison of lesion localization. ISUP, International Society of Urological Pathology; PZ, peripheral zone; CZ, central zone.

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tions compared to the histopathologically confirmed distribution in a heat map can be found within the online supplementary material (or all online suppl. material, see www.karger.com/doi/10.1159/000504266).

Discussion

There are studies reporting a limited additional value of SB in addition to TB [2, 22], but other authors also conclude that TB should be combined with SB for improved detection of clinically significant PCa [26–28]. However, the integration of MRI/US fusion into the diagnostic pathway in patients with suspicion for PCa with previous negative prostate biopsy led to an increased diagnostic accuracy for the detection of clinically significant PCa (Gleason score ≥3 + 4 = 7a (ISUP 2). Patients with suspicion for PCa and multiple negative prebiopsies are reported with heterogeneous detection rates in a random biopsy setting [15, 16, 29]. Extending the number of cores and locations may increase the diagnostic yield of PCa, but it may also inappropriately increase the detection of insignificant PCa, potentially leading to unnecessary treatments [11]. Conventional SB predominantly misses a potential proportion of PCa lesions located in the anterior segment of the prostate especially in patients with a reported increased number of anteriorly located PCa foci [30]. The results of our study with histologically 60% of pathologically confirmed anterior PCas strongly confirmed those data [25]. Therefore, we hypothesized that a modified standard 10 core template including 2 ventral (anterior) biopsies in addition to MRI/US fusion-guided biopsy in patients with ≥3 negative prebiopsies of the prostate would be beneficial for PCa detection.

Due to the results of the PRECISION trial [11], or the PROMIS group [12], or a large multicenter study of van der Leest et al. [13] a trend toward target biopsy as a primary approach for PCa detection can be observed. Patients with multiple negative prebiopsies before MRI might be rare in future. But according to the EAU guidelines [14], MRI is indicated in a repeat biopsy setting and SB is still indicated in addition to a TB. There are also little data about patients with multiple prebiopsies before TB. Our data seem to confirm that PCa lesions within these patients might predominantly be located anteriorly in both the MR images and also in the final histopathological samples. Based on our head-to-head comparison of histopathology and the associated imaging report after prostatectomy, still lesions have been either missed

by the MRI in 28.6% (6/21 cases) or rated false positively in 16.6% (3/18 cases). In contrast, the modified SB detected 90.5% of the PCa within in the anteriorly located lesions. The combination of the modified SB and TB detected both more clinically significant PCa and 100% [21/21] of the histopathologically classified anterior lesions.

A recently published study of Schouten et al. [31] reports high rates of missed PCa lesions in biopsy-naïve men by SB especially involving segments located anteriorly. The study also concludes to obtain additional samples from the anterior apex and anterior midgland during SB as a consequence of their findings. Hence, knowledge of lesions being missed with TB and SB is of clinical importance for diagnosis and treatment and needs further investigation. Our results demonstrate the importance of anterior biopsies during SB in pre-biopsied patients. These findings are also supported by the fact of a significant Gleason upgrade in the final pathology of anterior lesions despite biopsy modalities. However, adding SB to TB detected 5 more patients with significant PCa but also 9 insignificant PCa, potentially leading to overtreatment if active surveillance is not reasonably assessed.

Despite a positive role for the modified SB in PCa detection, we acknowledge further limitations to the present study. The study represents a single-center analysis without randomization, whereas multicenter randomized trials are desirable. Furthermore, the data set represents a highly selective patient cohort. Due to the awareness of the mpMRI, the urologist performing the SB might have resampled the respective areas during SB. Patients with a larger prostate volume might have been undersampled by a 10 core template [32]. Only patients with positive mpMRI (PI-RADS ≥3) findings have been included and mpMRI was lacking of DCE in 30 cases but according to PI-RADS version 2.0, DCE seems to be beneficial only in PI-RADS 3 lesions. Finally, we performed the biopsy transrectally, whereas patients with anteriorly located lesions could benefit from a perineal approach [33, 34]. Especially MRI-targeted perineal biopsy with in a repeat setting seems to increase the detection of PCa within the anterior zone [35].

Based on our study in hand, the combination of SB and TB seems to detect both more and clinically significant PCa. Furthermore, our cohort includes radical prostatectomy as the reference standard in most patients at least in our subgroup analysis and represents a good and strong association with an anterior localization of PCa foci in patients with multiple prebiopsies before imaging and consecutive TB.

Conclusion

Our study demonstrates a cumulative appearance of anterior PCa lesions in both mpMRI of the prostate and final histopathology in patients with multiple prebiopsies before TB and subsequent radical prostatectomy. The number of clinically significant cancer seems also be increased in these patients and especially within the anterior region. Mp-MRI is strongly indicated in patients referred for a repeat biopsy. Although associated with a significant proportion of Gleason upgrade in the final pathology, adding a modified systematic template biopsy with 2 additive ventral (anterior) biopsies seems to be beneficial to these patients.

Statement of Ethics

All enrolled patients signed a written informed consent for the intervention, data acquisition, data appraisal, and publication according to the Declaration of Helsinki and authorized by the institutional ethical review board of the Charité – Universitätsmedizin Berlin: EA1/283/14 and EA1/012/12.

Disclosure Statement

T.F. reports receiving honoraria as a speaker on national and international conferences for Siemens, Canon medical (Toshiba) and Hitachi, CEUS Advisory Board Member for Bracco. H.C. reports receiving honoraria as a speaker on national and international conferences for Hitachi. A.M. reports receiving honoraria as a speaker on national and international conferences for Canon medical (Toshiba). A.D.J.B. has received payments as a speaker for Bayer Pharma AG and b.e.imaging GmbH.

Author Contributions

A.M. and J.M.: designed the research study. A.M., C.S., H.C., A.D.J.B., A.M.N.: acquired the data. A.M., J.M., A.M.N., E.K., S.K.P., and C.-P.N.: analyzed the data. A.M., J.M., and A.M.N.: wrote the paper. C.S., H.C., T.F., J.B., A.D.J.B., and K.M.: critically revised the manuscript. A.M., C.S., T.F., and J.M.: supervised the study.

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