Aus dem
Charité Centrum 8 für Chirurgische Medizin
Klinik für Urologie, Campus Benjamin Franklin
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Habilitationsschrift

Implications of MRI/ultrasound fusion guided targeted biopsies on the diagnostics of prostate cancer

zur Erlangung der Lehrbefähigung
für das Fach Urologie

vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité-Universitätsmedizin Berlin

von

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Eingereicht: Januar/2017

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Table of Contents

Abbreviations

ACR	American College of Radiology
ESUR	European Society of Urogenital Radiology
GS	Gleason score
MRI	magnetic resonance imaging
mpMRI	multiparametric magnetic resonance imaging
PI-RADS	Prostate Imaging Reporting and Data System
PCa	prostate cancer
PSA	prostatic-specific antigen
TRUS	transrectal ultrasound
US	ultrasound

1. Introduction

In the developed countries, prostate cancer (PCa) is the cancer with the highest incidence and presents the third most common cause of male cancer related deaths [1]. Despite regional differences, the incidence of PCa is rising in most countries and the climb will further be accelerated by an aging population [2]. The PCa related mortality on the other hand is currently increasing in most countries [2]. Possible positive influences on PCa mortality might be improved therapeutic options and the use of serum prostatic-specific antigen (PSA) testing. In recent years the diagnostics of PCa and especially PSA testing was and is subject of critical discussions [3, 4]. The uncertainty regarding the benefits of PSA-based PCa screening was fueled by diverging results from two randomized PCa-screening trials [5, 6].

The American randomized prostate, lung, colorectal, and ovarian cancer (PLCO) screening trial concluded that there was no benefit in PCa related mortality after 10- and 13-years of follow-up [6, 7]. This lead to a recommendation by the U.S. Preventive Services Task Force against PSA-based PCa screening in 2012 [8]. Interestingly the subsequent reduction of PSA-testing in the US may have already lead to a stage shift towards high grade tumors [9]. A recent re-evaluation of the follow-up data of the PLCO trial showed that the control arm was heavily contaminated and that almost 90% of these men had at least one PSA test [10]. The American Urological Association (AUA) guideline does currently not fully abandon PSA-testing, but is more restrictive on the patients age than other guideline and “strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences” [11].

The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial on the other hand, showed a 27% risk reduction of PCa mortality at a 13-year follow-up, but this came at the expense of a possible over-diagnosis and overtreatment [12]. The PCa guideline of the European Association of Urology (EAU) reflects this data in stating that a population-wide screening is not indicated, but an early cancer diagnosis based on an individual strategy is recommended starting at the age of 40 years [13].

An additional incorporation of PCa-risk nomograms in the individual decision process can increase the predictive value of PSA-testing [14]. The current corner stones for the early PCa detection as advised by the German and European guidelines are digital rectal examination (DRE), serum PSA and if suspicious are followed by an transrectal ultrasound (TRUS)-guided 10-12 core systematic prostate biopsy [13, 15]. The predictions of the European cancer mortality for the year 2016 showed an 8% reduction for PCa since the year 2011 [16]. Besides the improvements in PCa therapy, the authors stated that PCa screening might have also influenced this positive trend [16].

As stated above, either an elevated serum PSA (also free/total PSA ratio, PSA velocity and PSA density) or suspicious DRE currently present the recommended triggers for a prostate biopsy. The standard systematic prostate biopsy presents an organ based biopsy regimen according to the prostatic zonal anatomy and is mostly aimed at the peripheral zone of the prostate. Hodge et al. first introduced a sextant systematic TRUS-guided biopsy in 1989 [17]. The sextant regimen did not include the dorsolateral zones of the prostate and therefore the extended biopsy regimen with 10-12 cores were introduced around the year 2000 [18, 19]. The cancer detection rate of the primary systematic prostate with 10 to 12 biopsy cores ranges from 31 to 48% and trials comparing both transrectal and transperineal biopsy approaches reported similar results [20-24]. Efforts to improve the cancer detection rate by further increasing the number of biopsy cores lead to a higher detection of insignificant cancers, although a higher overall cancer detection was shown [25, 26]. Another study be Pepe et al. showed that a primary transrectal saturation biopsy with a median of 29 biopsy cores did not improve the PCa detection rate significantly compared to a primary 12-core biopsy [27]. Therefore, the 10-12 core systematic biopsy currently remains the standard approach for the primary biopsy setting as recommended by the German and European urological guidelines [13, 15].

After a negative primary biopsy, the risk of a false negativity remains and patients may therefore undergo multiple repeat biopsies often based on persistently elevated or rising serum PSA-values [28]. In the repeat biopsy setting, the cancer detection rate of

the 10-12 core systematic biopsy further decreases from 29% in the first repeat biopsy to 11% in the fourth repeat biopsy [28]. Nonetheless, these patients may still harbor significant PCa and many patients may experience numerous prostate biopsies. In the repeat biopsy setting the saturation biopsy was and still is considered a viable option [29]. In the study of Pepe et al. the saturation biopsy in the patients with prior negative biopsy was superior to a 18 core or 12 core biopsy regimen [27].

In the repeat biopsy setting the sampling of the transitional zone of the prostate was emphasized in a critical review of biopsy techniques [29]. Another option presents a transperineal template guided biopsy, using a brachytherapy grid. In two studies published in 2007, the template mapping biopsy with 21 to 50 biopsy cores were taken in men with prior negative biopsies, the cancer detection rate was 37% and 42% [30, 31]. The improved cancer detection especially at the apex and the ventral aspect of the prostate comes at the cost of a higher invasiveness and the need of spinal or general anesthesia.

Further efforts were made to improve the accuracy of the TRUS-guided biopsy without necessarily increasing the number of biopsy cores. In addition to the standard B-mode image, the value of a tissue elastography and contrast enhanced ultrasound (US) techniques and their value in PCa detection were studied. In a study including 259 men, Boehm et al. showed that adding elastography guided targeted biopsies to systematic biopsy lead to an increased concordance of the biopsy Gleason score (GS) to the final GS after radical prostatectomy [32]. Conversely, another single center study including 679 men with primary and repeat biopsies, who received elastography guided biopsies in addition to a systematic biopsy concluded a “limited reliability” for the elastrography to predict PCa detection [33]. Another possible option to improve the visibility of a cancerous lesion on US is contrast enhanced US which uses a microbubble contrast agent [34]. Although an improved cancer detection with contrast enhanced US guided targeted biopsies in addition to a systematic biopsy were reported, two prospective trials did not show an additional benefit of contrast enhanced US guided biopsies compared to a systematic biopsy [35-37]. The current German guideline gives a clear

statement against the use of elastography and contrast enhanced US in the primary diagnostics of PCa [15].

Besides the possible deficits of the TRUS guided systematic prostate biopsy, there are uncertainties concerning the grading accuracy of the biopsy GS, influenced by sampling variation and interobserver variability of the pathologist [38-40]. Despite the underlying challenges in PCa diagnostics, clinical decisions have to be based on the available data (biopsy histology, serum PSA and DRE). This concludes the necessity to improve the diagnostic tools leading to greater accuracy, increased detection of clinically significant PCa and reduction of unnecessary prostate biopsies.

For years, imaging modalities such as computed tomography or magnetic resonance imaging (MRI) were no integral part of PCa diagnostics. The emergence of multiparametric magnetic resonance imaging (mpMRI) of the prostate may now lead to a paradigm shift, initiating new options for the diagnosis and treatment of PCa, such as targeted biopsies or a targeted therapy. MpMRI is defined by T2 weighted image (T2WI) in combination with at least two of the following sequences; dynamic contrast enhanced MRI (DCE), diffusion weighted imaging (DWI), magnetic resonance spectroscopic imaging (MRSI) [41-43]. A mpMRI can be performed on 1.5 Tesla and 3 Tesla MRI scanners with or without an endorectal coil, the 3 Tesla MRI providing an enhanced image quality due to a higher signal-to-noise ratio [44]. Studies correlating mpMRI with radical prostatectomy specimen showed a high sensitivity for significant PCa [45-48]. Based on these studies, the European and German guidelines updated their recommendations in 2014 to include mpMRI as a diagnostic option for patients with previously negative prostate biopsies [13, 15]. The European Society of Urogenital Radiology (ESUR) published the first guideline for a standardized evaluation and documentation of mpMRI of the prostate in 2012 [41]. The ESUR guideline, that was derived from the Breast Imaging Reporting and Data System (BI-RADS) for mammography findings, introduced the Prostate Imaging Reporting and Data System (PI-RADS) based on review of the literature and expert consensus [41].

The PI-RADS version 1 comprises a sum score of the included sequences (T2WI for peripheral and transition zone, DCE, DWI, MRSI) as well as an overall Likert-like grading for the suspicion of each lesions, defined as followed [41]:

PI-RADS Score 1 = Clinically significant disease is highly unlikely to be present

PI-RADS Score 2 = Clinically significant cancer is unlikely to be present

PI-RADS Score 3 = Clinically significant cancer is equivocal

PI-RADS Score 4 = Clinically significant cancer is likely to be present

PI-RADS Score 5 = Clinically significant cancer is highly likely to be present

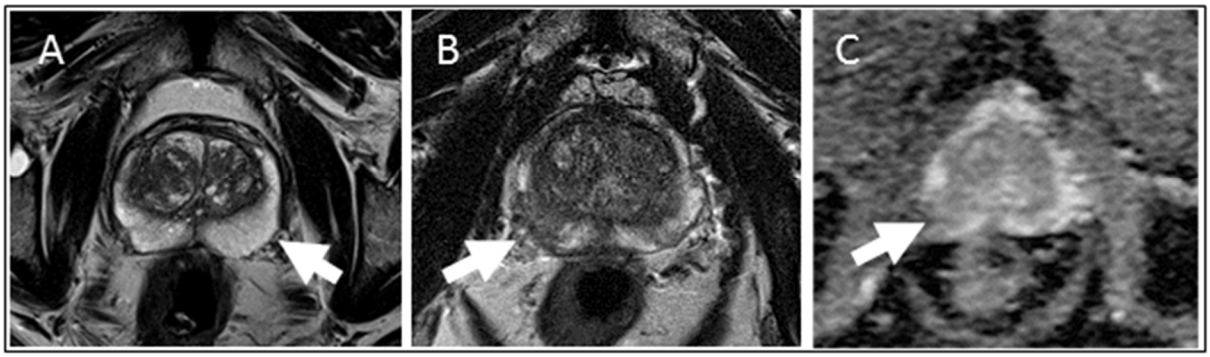

Fig. 1 (A) Example of PI-RADS score of 1T2-weighted image of a normal peripheral prostatic zone and central benign hyperplasia. (B/C) Example of a PI-RADS score 2 lesion. (B) Stripy bilateral changes in peripheral zone on the T2-weighted image. (C) The apparent diffusion coefficient (ADC-map) shows a mild diffusion restriction in analogy to the finding on the T2-weighted image.

At the time of publication of the ESUR guideline, there was no clinical data verifying the proposed PI-RADS scoring. In 2015 an updated PI-RADS classification (also referred to as PI-RADS version 2) was published in collaboration of the ESUR, the American College of Radiology (ACR) and the AdME Tech foundation [49]. In the PI-RADS version 2 the above stated definitions of the PI-RADS scores remained unchanged [49]. Version 2 implemented a categorical scoring system giving a single MRI sequence more importance according to the zonal location of the suspicious lesion. This presents a major difference to PI-RADS version 1, which used a sum score of all MRI sequences

to grade the prostatic lesion. Furthermore, PI-RADS version 2 introduced a cut-off of ≥15mm for the maximal lesion size defining a PI-RADS 5 lesion (unless extraprostatic extension of the lesion is present).

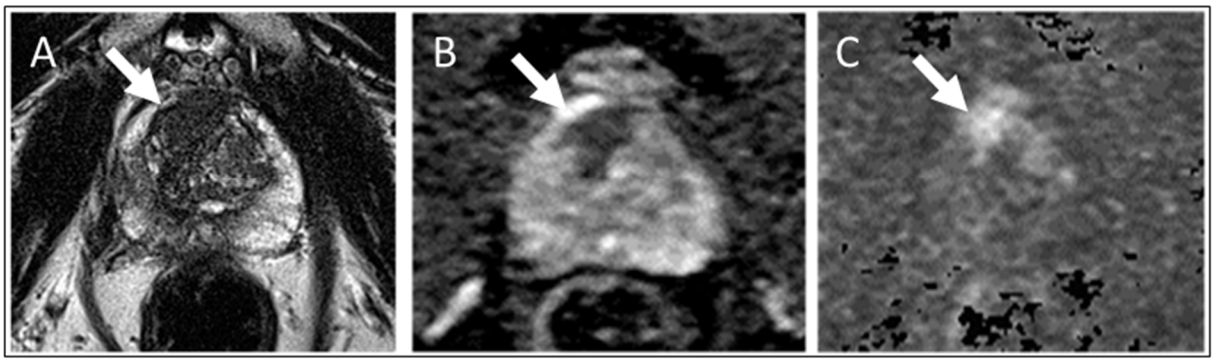

Fig. 2 Example of a PI-RADS 5 lesion. The patient had received a negative systematic biopsy at PSA 11ng/ml. Six months later at PSA 17ng/ml a mpMRI is performed. (A) T2-weighted image shows an erased charcoal sign of the anterior transitional zone of >15mm diameter. (B) ADC-map showing a strong diffusion restriction (low signal intensity) in analogy to the T2-weighted image showing even clearer the suspicious lesion. (C) The corresponding high b-value image shows marked diffusion restriction (high signal intensity) in the anterior transitional zone.

The mpMRI presents the basis for a targeted biopsy either as in-bore MRI guided biopsy or as MRI/US fusion guided targeted biopsy.

An in-bore MRI guided biopsy is performed with real-time MRI guidance and direct targeting of the suspicious lesion within the prostate. Only a limited number of targeted biopsy cores are taken and no random biopsy of the prostate is performed. The procedure may take one to two hours, leading to a higher cost of an in bore MRI guided biopsy and is a higher burden for the patient who has to remain in a prone position for a long period of time [50].

MRI/US fusion guided targeted biopsy can be performed as cognitive registration, 3D software-based registration, sensor-based registration or as sensor-based registration with software-aided biopsy planning [51]. Cognitive fusion referrers to the physician conducting a TRUS-guided biopsy, aiming at the suspicious lesion only in knowledge of the mpMRI result, but without factual co-registration of the MRI and TRUS image.

The software-based fusion creates both a 3D TRUS and a 3D MRI volume of the prostate, which are then co-registered and used for targeted biopsy. Software-based registration platforms offer either a rigid registration or an elastic registration, where the deformation of the prostate by the US probe is computed for the 3D prostate volume. The sensor-based registration allows a movement tracking of the US probe through a magnetic sensor. Axial or sagittal MRI and TRUS planes are co-registered according to anatomical landmarks.

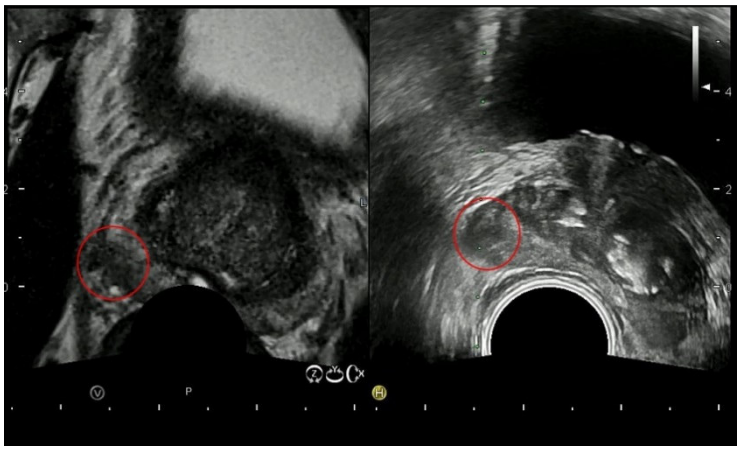

Fig. 3 Example of a sensor based MRI/US fusion biopsy. According to anatomic landmarks the MRI and US images are fused. (Left) MpMRI shows a PI-RADS 4 lesion in the right peripheral dorsolateral zone. (Right) In the real-time US image targeted biopsies were obtained from the target lesion revealing a Gleason 3+4=7 PCa.

Delongchamps et al. compared the performance of systematic biopsies to targeted biopsies acquired by cognitive fusion targeted biopsy, sensor-based targeted biopsy and software-based targeted biopsy. The study showed similar results for systematic biopsy and cognitive targeted biopsy and improved cancer detection rates for both sensor- and software-based targeted biopsy [52]. First results of MRI/US fusion guided targeted biopsy in the pre-PI-RADS era were published by Vourganti et al. in 2012 [53]. The study included 195 men with prior negative prostate biopsies showed a cancer detection rate of 37% and detected more clinically significant PCa [53]. The authors concluded that MRI/US guided targeted biopsy was not susceptible to the decreasing cancer detection rate of untargeted repeat biopsies and most appropriate for patients with remaining PCa suspicion after primary systematic biopsy.

At our institution, first imaging studies on prostate MRI were published in 2005 and initial experiences with an in-bore MRI guided targeted biopsy was also described in 2005 [54, 55]. The first larger series of men with prior negative systematic biopsy undergoing in-bore MRI guided targeted biopsy was initiated in 2008 and published 2011 [42]. The MRI/US fusion guided targeted biopsy was established in 2012 with a sensor based fusion platform, in collaboration of urologists and radiologists [42, 56]. The initial results in 32 patients were promising and the cancer detection rate was comparable to the study of Vourganti et al. [53, 56].

1.1 Study Objective

This ‘habilitation’ thesis is aimed to discuss the influence, value and performance of mpMRI and MRI/US fusion guided targeted biopsy in the detection of PCa and the future implications on how to diagnose PCa. All patients were treated at Charité Universitätsmedizin Berlin, Berlin, Germany.
The included publications deal with the following objectives:

- Evaluating the performance of MRI/US fusion guided targeted biopsy in combination with a 10-core systematic biopsy to detect PCa and to analyze the influence of the number of prior negative biopsies on the cancer detection rate.

- Correlation of the PI-RADS scores with cancer detection on MRI/US fusion guided targeted in combination with a 10-core systematic biopsy.

- Investigating the reasons for target biopsy failure in the subgroup of men, where cancer was only detected by systematic biopsy and MRI/US fusion guided targeted biopsy was negative for PCa.

- Analyzing the added value of a sagittal image fusion to the standard axial image fusion in a sensor based MRI/US fusion guided targeted biopsy

- Identifying men where a MRI/US fusion guided targeted biopsy without an additional systematic biopsy is sufficient and evaluating the predictors for a prospective patient stratification for a sole targeted biopsy.

2. Own work – original articles

2.1 Performance of MRI/US fusion guided targeted biopsy

Maxeiner, A.;Stephan, C.;Fischer, T.;Durmus, T.;Kilic, E.;Asbach, P.;Haas, M.;Gunzel, K.;Neymeyer, J.;Miller, K.; Cash, H. [Real-time MRI/US fusion-guided biopsy in biopsy-naive and pre-biopsied patients with suspicion for prostate cancer]. Aktuelle Urol. January/2015 34-3846(1)

The study focused on the performance of MRI/US fusion guided targeted biopsy combined with a 10-core TRUS guided systematic biopsy to detect PCa. Further we analyzed the related the cancer detection rate to the number of prior negative TRUS-guided biopsies. In 310 patients with at least one suspicious lesion (defined by the PI-RADS classification) on mpMRI underwent targeted biopsy in combination with systematic biopsy between January 2012 and July 2014. The maximal PI-RADS score in each patient was distributed as followed: PI-RADS 2 10% (32 patients), PI-RADS 3 31% (95 patients), PI-RADS 4 35% (109 patients) and PI-RADS 5 24% (74 patients). The cohort included 53 patients (17%) with no prior negative biopsy, 91 patients (29%) with one prior negative biopsy, 98 patients (32%) with two prior negative biopsies and 68 patients (22%) with three and more prior negative biopsies. The total detection rate was 51% (158 patients) (51%) and the GS distribution was GS 6 in 60 patients (38%), GS 7 in 54 patients (34%) and GS ≥8 in 44 patients (28%). The analysis of the 158 cancer positive men showed, that 110 cases (70%) were diagnosed by the combination of targeted biopsy and systematic biopsy and 48 cases (30%) were diagnosed by the systematic biopsy alone. In men where PCa was diagnosed only by the systematic biopsy the rate of GS ≥8 was lower (15% vs. 34%) and the rate of GS 6 was higher (54% vs 31%).

Regarding the number of previously negative biopsies, the detection rate was 75% (40 patients) for the primary biopsy with a rate of GS ≥ 7 of 75%. The detection rate for men with one to more than three negative biopsies was 54% (49 patients), 51% (39 patients) and 44% (30 patients), respectively. The rate of GS ≥ 7 was 69% in patients with one, 49% for patients with two and 50% for patients with ≥ 3 prior negative biopsies. A multivariate analysis showed PSA-levels and the PI-RADS score to be strong predictors

for the detection of PCa with a GS ≥ 7 (p-value 0.007 PSA; p-value ≤0.001 PI-RADS score).

The combination of targeted biopsy with systematic biopsy diagnosed a high rate of significant PCa and showed an improved overall cancer detection compared to the standard systematic biopsy. Although men with prior negative biopsies had a lower rate of significant PCA, the overall detection rate was greatly improved. The positive results in men undergoing primary targeted biopsy need further validation in a larger cohort. The PI-RADS score of the suspicious lesion presents a predictor for the detection of clinically relevant PCa and needs to be further evaluated.

Maxeiner, A. et al.: [Real-time MRI/US fusion-guided biopsy in biopsy-naive and pre-biopsied patients with suspicion for prostate cancer]. Aktuelle Urol. 2015 Jan;46(1):34-8.
https://doi.org/10.1055/s-0034-1395563

2.2 The influence of the PI-RADS score in the detection of clinically significant prostate cancer

Cash, H.;Maxeiner, A.;Stephan, C.;Fischer, T.;Durmus, T.;Holzmann, J.;Asbach, P.;Haas, M.;Hinz, S.;Neymeyer, J.;Miller, K.;Gunzel, K.;Kempkensteffen, C. The detection of significant prostate cancer is correlated with the Prostate Imaging Reporting and Data System (PI-RADS) in MRI/transrectal ultrasound fusion biopsy. World J Urol. April/2016;34(4):525-32.

The PI-RADS classification was introduced by the ESUR in 2012, but data on the detection rate and the GS associated with the PI-RADS score of the suspicious lesion on mpMRI was limited to a few studies [57-59]. Our prospective cohort study evaluated 408 patients who received a MRI/US fusion guided targeted biopsy combined with a 10-core TRUS guided systematic biopsy between January 2012 and January 2015. The objective of the analysis was to show the cancer detection rate, GS, the rate of clinically significant PCa and histology after radical prostatectomy in relation to each PI-RADS score. In addition a correlation of the cancer detection rate to the number of prior negative biopsies was performed.

Overall, 56% of men (227/408) were diagnosed with PCa. The cancer detection rate was 74% (60/81) for men undergoing primary biopsy. Men with one, two and greater or equal of three prior biopsies showed detection rates of 57 % (67/117), 49 % (62/126) and 45 % (38/84), respectively. Despite the declining cancer detection with the increasing number of previous biopsies, the rate of significant PCa detected stayed stable (76-79%). Apportioning the PCa detection to each PI-RADS score (patient based analysis) showed a cancer detection rate of 16% (5/32) for lesions with PI-RADS 2, 26% (29/113) for PI-RADS 3, 62% (94/152) for PI-RADS 4 and 89% (99/111) for PI-RADS 5. The rate of significant PCa increased with a higher PI-RADS score, with 95% of detected cancers being clinically significant for PI-RADS 5. In the multivariate analysis, PI-RADS was the strongest predictor for the detection of significant PCa. When compared to targeted biopsy alone, the combination of targeted biopsy with systematic biopsy lead to an improved detection rate of 10-20% depending on the PI-RADS score, but also lead to more insignificant PCa. A sole targeted biopsy would

have missed 18% (47/227) significant cancers, detected by the additional systematic biopsy. For 61% (139/227) of cases, the histology after radical prostatectomy was available. Here men with PI-RADS 4 and 5 had a ≥pT3 PCa in 20% (11/56) and 49% (32/65).

The combination of MRI/US fusion guided targeted biopsy with a 10-core TRUS guided systematic biopsy leads to an increased detection of significant PCa in men with initial and repeat prostate biopsies. The higher rate of significant cancer was correlated to increasing PI-RADS scores. Men with lesions rated PI-RADS 4 or 5 on mpMRI are also more likely to show an adverse pathological stage after radical prostatectomy.

Cash, H.; et al.: The detection of significant prostate cancer is correlated with the Prostate Imaging Reporting and Data System (PI-RADS) in MRI/transrectal ultrasound fusion biopsy. World J Urol. April/2016; 34(4):525-32

https://doi.org/10.1007/s00345-015-1671-8

2.3 Reasons for targeted biopsy failure

Cash, H.;Gunzel, K.;Maxeiner, A.;Stephan, C.;Fischer, T.;Durmus, T.;Miller, K.;Asbach, P.;Haas, M.;Kempkensteffen, C. Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure. BJU Int. July/2016;118(1):35-43.

The aim of the study was to identify possible reasons for the failure of MRI/US fusion guided targeted biopsy. We therefore reviewed the data of 408 patients who had received a MRI/US fusion targeted biopsy biopsy in combination with a 10-core TRUS-guided systematic biopsy between January 2012 and January 2015. Sixty-one men with cancer detection only by systematic biopsy and a negative targeted biopsy were included into the retrospective analysis.

The mpMRI of each patient was re-evaluated in a blinded consensus reading by two experienced radiologists according to the PI-RADS classification. Subsequently, an unblinded anatomical correlation of the suspicious lesion described on mpMRI and the biopsy result was performed and the potential reasons for the failure of the targeted biopsy were analyzed. The PCa detected by systematic biopsy was significant in 39 of 61 patients (64%) according to the Epstein criteria or intermediate-/high-risk PCa in 35 of 61 patients (57%) as per EAU guideline. Overall 90 cancer suspicious lesions were re-evaluated and the blinded consensus reading lead to a downgrading of the initial PI-RADS score in 45 of 90 lesions (50%). A PI-RADS upgrading was noted in 13 of 90 lesions (14%). One possible explanation for a negative targeted biopsy was a “falsely high initial PI-RADS score” (defined by a downgrade to a PI-RADS score ≤ 2 in the re-reading) which was assigned to 31 lesions (34%). For 36 lesions (40%) in 35 patients (57%), the anatomical localization of the positive biopsy core of the systematic biopsy could be correlated to the localization of the lesion on mpMRI. When the target lesion was sampled in the systematic biopsy, the lesions were mostly rated as PI-RADS 4 or 5 and had a GS of ≥ 7. In addition, the unblinded correlation of the mpMRI to the positive

biopsy cores in systematic biopsy revealed 70 lesions in 44 patients, where even retrospectively no lesion on mpMRI was definable. In these invisible lesions, 67% of the biopsy cores detected Gleason 6, but five of 70 lesions (7%) were Gleason ≥ 4+3, which would have been missed without the additional systematic biopsy.

The study concluded that the most observed reason for the failure of targeted biopsy was an error within the targeted biopsy. The second reason was a “falsely high PI-RADS score” leading to a negative sampling of the targeted biopsy. In addition, mpMRI of the prostate missed a small number of clinically significant PCa. Thus, the systematic biopsy detects a large number of significant PCa despite a negative targeted biopsy and may compensate for a possible targeted biopsy error. Therefore, the targeted biopsy should currently be combined with a systematic biopsy.

Cash, H. et al: Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure.

BJU Int. July/2016; 118(1):35-43.

https://doi.org/10.1111/bju.13327

2.4 Added value of a sagittal image fusion in a sensor-based MRI/US fusion guided biopsy

Günzel K.;Cash H.;Buckendahl J.;Königbauer M.; Asbach P.; Haas M.;Neymeyer J.;Hinz S.;Miller K.;Kempkensteffen C. The addition of a sagittal image fusion improves the prostate cancer detection in a sensor-based MRI /ultrasound fusion guided targeted biopsy. BMC Urology, January/2017, 17(1):7.

When performing a sensor-based MRI/US image fusion, the standard is to synchronize both the MRI and the US image in the axial plane before biopsying the target lesion. In the previous study, we had evaluated the possible targeting errors, which raised the question of how to improve the image fusion. In this study, we therefore analyzed the added value of an image fusion in the sagittal plane in the detection of PCa, without increasing the total number of taken biopsies.

The retrospective analysis included 251 patients with a suspicious mpMRI (PI-RADS ≥3) who received a MRI/US targeted biopsy in combination with a ten core systematic biopsy between July 2013 and September 2015. The biopsy was performed on a sensor based US fusion system. The patients were divided into two groups. Group A (n=162) included men where the targeted biopsy was executed after an axial MRI/US image fusion. In Group B (n=89), the men received a targeted biopsy in both an axial and sagittal MRI/US image fusion. The median age and PSA-levels were comparable between the two groups. There was an imbalance between the two groups concerning a positive digital rectal examination (14% vs. 29%, p=0.007) and the number of men undergoing a primary MRI/US targeted biopsy (33% vs 46%, p=0.046). The PCa detection rates stratified according to each PI-RADS score in group A were: PI-RADS 3 42 %, PI-RADS 4 48 %, PI-RADS 5 75 %; the detection rates in group B were: PI-RADS 3 25 %, PI-RADS 4 74 %, PI-RADS 5 90 %. The proportion of GS ≥7 that was missed by MRI/US targeted biopsy was 8% lower in group B (group A 15% vs group B 7%). The multivariate binary logistic regression analysis showed that the PI-RADS score, a suspicious digital rectal examination DRE and an added sagittal image fusion

were significant predictors for cancer detection on targeted biopsy. The added sagittal image fusion detected nine men (10%) where cancer was detected only by sagittal targeted biopsy. A Gleason upgrading leading to the detection clinically significant PCa (Gleason ≥ 7) in the cores acquired by the sagittal targeted biopsy was found in 10 men (11%). Adding a sagittal image MRI/US fusion to the biopsy protocol without increasing the total number of biopsy cores seems to improve the effectiveness of a sensor-based MRI/US fusion biopsy.

Günzel K. and Cash H. et al. The addition of a sagittal image fusion improves the prostate cancer detection in a sensor-based MRI /ultrasound fusion guided targeted opsy. BMC Urology, January/2017, 17(1):7.

https://doi.org/10.1186/s12894-016-0196-9

2.5 Predictive factors for equal or superior performance of a sole targeted biopsy

Günzel K.;Haas M.; Maxeiner A.;Stephan C.;Buckendahl J.;Asbach P.;Miller K.;Kempkensteffen C.;Cash H. Predictive Parameters Identifying Men Eligible for a Sole MRI/Ultrasound Fusion-Guided Targeted Biopsy without an Additional Systematic Biopsy. Urol Int. September/2016 [Epub ahead of print]

Multiparametric MRI of the prostate and the possibility of targeting the suspicious area have generated the concept of a sole fusion-guided targeted biopsy without the addition of a systematic biopsy. The analysis was aimed to identify predictive clinical parameters slecting men suitable for a sole MRI/US targeted biopsy. Between August 2013 and July 2015, 251 consecutive men who underwent a sensor-based, real-time MRI/US targeted biopsy in combination with a 10-core systematic biopsy. The univariate and multivariate binary regression analysis, in this retrospective study, identified predictors for the maximal PCa risk group detection by targeted biopsy compared to an equal or lower risk group detected by the systematic biopsy.

The cancer detection rate for targeted biopsy was 63% (157/251) and 70% (176/251) for systematic biopsy. The combination of targeted biopsy and systematic biopsy lead to a cancer detection in 77% (193/251) of patients. Analyzing the number of cancer positive cores showed that 50% (291/584) of targeted biopsy cores were positive and 22% (539/2486) of cores acquired by systematic biopsy revealed cancer. In the univariate regression analysis predictors for equal/superior performance of a sole targeted biopsy were lesion size (maximal diameter; OR 1.050, 95% CI 1.002-1.101, p = 0.043), suspicious digital rectal examination (DRE; OR 2.448, 95% CI 1.062-5.645, p = 0.036) and free/total prostate-specific antigen (PSA) ratio (f/t PSA ratio) ≤0.15 (OR 0.916, 95% CI 0.867-0.967, p = 0.002). In the multivariate analysis only f/t PSA ratio ≤0.15 (OR 0.916, 95% CI 0.867-0.967, p = 0.002) showed to be a significant predictor for a sole targeted biopsy. The combination of all three predictors identified only 14 men where a sole targeted biopsy approach would have saved 187 biopsy cores. The combination of the lesion size (of the PI-RADs rated lesion) with f/t PSA ratio included 70 men, where omitting the systematic biopsy would have saved 700 biopsy cores with

the risk of missing two (4%) high risk PCa and underestimating the risk group in three (6%) men.

The analysis demonstrates possible criteria on which patients may be counseled regarding a possible sole targeted biopsy without risking to underestimate the final PCa risk group.

Günzel et al. Predictive Parameters Identifying Men Eligible for a Sole MRI/Ultrasound Fusion-Guided Targeted Biopsy without an Additional Systematic Biopsy.

Urol Int. 2017;98(1):15-21.

https://doi.org/10.1159/000449258

3. Discussion

Within the last four years increasing data on the performance of mpMRI of the prostate and the successive MRI/US fusion guided targeted biopsy have been published. Based on the studies available at the time of preparation of the current German guideline (an update is soon to be published) and European PCa guidelines have included a positive statement on mpMRI for men with prior negative biopsies [13, 15]. In case of a repeat biopsy the diagnostic value of an mpMRI is higher than other available analytic tests as the prostate cancer gene 3 test or prostate health index (PHI) [62]. The increased use of mpMRI in the diagnostics of PCa was accompanied with the introduction of a standardized reporting system of cancer suspicious lesions within the prostate - PI-RADS - in 2012 [41]. An updated and simplified version of PI-RADS was published in 2015, but a large scale comparison of both versions has to this date not been published [49]. Currently most published studies were rated according to PI-RADS version 1 and the impact of version 2 is yet to be shown.

The performance of MRI/US fusion biopsy

When the sensor-based MRU/US fusion guided biopsy was initiated in our institution, data was scarce, but first results of our working group were promising [56]. For the sensor-based image fusion a low-range magnetic field is created by a transducer placed next to the patient's pelvis [56]. Within this magnetic field, a sensor attached to the US probe that could be tracked by the US platforms' software. Once the MRI and the real-time US images are fused according to anatomic landmarks, the MRI image will follow the movements of the US probe, including the angulation of the probe (please also see Figure 3). With increasing adoption of a mpMRI prior to an indicated prostate biopsy, more patients were referred to targeted biopsies by the treating urologist. Thus, we were able to analyze 310 men who received a sensor based MRI/US fusion guided targeted biopsy in combination with a 10-core systematic biopsy. The overall cancer detection rate was 51% and showed a clear improvement to our initial results (cancer detection rates 38% and 39%) [56, 63, 64]. The cancer detection rate was also in line with published data, although all biopsies were performed with different MRI/US fusion platforms [65-67]. For the 53 men with a primary targeted biopsy that were also included

into the analysis, the cancer detection rate was 75%. Other groups described similar rates (64-70%) in cohorts of 51 to 142 men [66, 68]. Overall, the data showed the improved cancer detection of targeted biopsy in the primary and repeat biopsy setting compared to standard biopsy [20-24, 28]. This was also the case if the men had ≥ prior negative TRUS-guided biopsies. Besides the increases overall cancer detection, MRI/US fusion guided targeted biopsy showed a GS ≥7 in 75% of men with primary targeted biopsy and 50% of men with ≥3 prior negative biopsies [63]. Habchi et al. and Pokorny at al. published complementary trends towards a higher detection of GS ≥7 PCa by targeted biopsy [65, 68]. Despite the mentioned improvements by MRI/US fusion biopsies, these results were achieved when adding a 10-core systematic biopsy. In 15% on men in our study cohort PCa was solely detected by the systematic biopsy. In this subgroup, 54% of biopsies were GS 6, but the targeted biopsy would have also missed 14% of clinically significant PCa. Salami et al. evaluated the need for an additional 12-core systematic biopsy in a cohort of 140 men who underwent a MRI/US fusion targeted biopsy in a repeat biopsy setting [59]. Targeted biopsy missed 20% of tumors, but only 4.4% were clinically significant. The authors nonetheless concluded that the systematic biopsy “may be needed” in order not to miss some relevant cancer [59]. Overall, our study in a large cohort of men showed that a sensor-based MRI/US fusion biopsy in combination with a systematic biopsy could detect a large rate of clinically significant PCa in both the primary and repeat biopsy setting.

The influence of the PI-RADS score on cancer detection

In 2012 the ESUR introduced PI-RADS as a standard of reporting for suspicious lesions on mpMRI [41]. The PI-RADS scores lesions suspicious for PCa on mpMRI on a scale of 1-5 and it seemed obvious that higher scores would lead to a higher cancer detection on targeted biopsy and would include more significant PCa. However, a meta-analysis on PCa detection by mpMRI, which screened 109 studies published on the topic until March 2013, stated that only 14 studies applied PI-RADS scoring [69]. Nonetheless, the meta-analysis included 1785 men and the calculation for the overall significance of the PI-RADS scoring stated a sensitivity of 0.78 and specificity of 0.79 for the detection of cancer. The negative predictive values varied from 0.58 to 0.95. The meta-analysis showed, that PI-RADS had a “good diagnostic accuracy” but no conclusion on the

single PI-RADS scores and the optimal cutoff was be given due to the heterogeneity of the published data [69].

This lead to the rationale to correlate the cancer detection rate to each PI-RADS score. At the time of publication, our study included the largest cohort, in which the cancer detection rate in relation to each PI-RADS score was analyzed (408 patients). The patient based analysis (combination of targeted biopsy with systematic biopsy) showed that the cancer detection rate for men with a PI-RADS 2 lesion was 16%, for PI-RADS 3 the cancer detection rate was 26%. For PI-RADS scores 4 and 5 the cancer detection rate was 62% and 89% [60]. At the time of publication of our data, three studies that included 105 to 294 patients, also reported the cancer detection in correlation to each PI-RADS score [57-59]. Overall, the detection rates were comparable but e.g. for PI-RADS 5, the cancer detection rate ranged from 70 to 100% [57-59]. The number of prior negative biopsies is known to influence the cancer detection rate on standard systematic biopsy and despite an overall improvement by the added targeted biopsy may still influence the performance of MRI/US fusion guided biopsy [28, 53, 59, 70, 71]. In our cohort, there was a declining cancer detection rate in men with one prior biopsy (57%) to men with ≥3 negative biopsies (45%), but the combination of targeted biopsy with systematic biopsy was still able to detect 76-79% of significant PCa. Although the detection rate and rate of significant cancers were lower, Vourganti et al. and Sonn et al. showed a similar trend of improved diagnostic accuracy in men with prior negative biopsies [53, 71]. For PI-RADS 3 lesions, the detection rate was 29% with 59% of these cancers showing GS 6 on histopathology. This raises the question men with a PI-RADS 3 lesion may be further counseled if a biopsy is really warranted. In a cohort of 282 men with repeat MRI/US fusion biopsy, De Luca et al. showed that especially in men with a PI-RADS 3 lesion, a suspicious prostate cancer gene 3 urine test lead to higher Gleason grades [72]. When correlating the PI-RADS scores to the rate of significant PCa in all patients, we found that the higher PI-RADS score 4 and 5 strongly associated with superior rates of significant PCa (74% and 95%). This finding was in line with previously published studies where targeted biopsy lead to an improved detection of significant PCa compared to systematic biopsy alone [53, 59, 70, 71]. These studies also showed that the combination of targeted biopsy with systematic biopsy yielded the best results. This was again the case in our larger cohort, although the targeted biopsy alone still lead to higher detection rates of PCa than standard systematic biopsy.

Nonetheless, 28% of all cancers and 18% of significant PCa would have been missed without the additional systematic biopsy. Other studies on targeted biopsy, reported rates of missed PCa of 16.5% to 26% and missed significant PCa of 4% to 12%, but the definition of significant PCa varied among the studies [58, 59, 70]. The authors of these studies concluded, that currently targeted biopsies should be combined with a systematic biopsy, which was also our recommendation.

Reasons for targeted biopsy failure

The rate of cancers missed by targeted biopsy lead to a further analysis of this subgroup of patients [61]. At the time of publication, our data presented the first assessment of possible reasons for the failure of targeted biopsy. The study included men where cancer was only detected by systematic biopsy and the targeted biopsy was negative. The main cause for a negative targeted biopsy was that the targeted biopsy had missed the targeted lesion. The biopsy core of the systematic biopsy was retrospectively matched to the target lesion in 57% of men. The target lesions that were sampled by the systematic biopsy consistent mainly of GS ≥7, PI-RADS scores ≥4 and a median lesion size of 15mm. Since the MRI/US fusion platform does not offer automated needle tracking and therefore deviation of the biopsy needle are unknown, the underlying reason for the targeted biopsy-failure remained unknown. Data on the target registration error acquired by software-based image fusion showed that the error ranged from 2 to 4.3mm [73-76]. Baumann et al. tested the value of elastic registration compared to a rigid registration in a computed setting and concluded a reduced target registration error (2mm in elastic vs. 3mm in rigid image registration) [75]. These studies only focused on the co-registration of the MRI and US images and prostate deformation or movement in an actual prostate biopsy were not taken into account. Westhoff et al. showed in an ex vivo model that targeted biopsies may vary 0.14-10.6mm from the center of the target depending on the MRI/US fusion system used for the targeted biopsy [77].

The other reason for a negative targeted biopsy was a “falsely high initial PI-RADS score”, determined by a blinded consensus re-reading of two experiences radiologists. A PI-RADS score downgrading was observed in 50% of the lesions and in 32% of the

lesions, this being the reason for the negative targeted biopsy. As previously shown, lesions described on mpMRI as PI-RADS 2 or 3 are often benign [57, 58, 60]. The likelihood of a downgrading of the initial rating was higher if an inexperienced reader (< 2 years' experience for prostate MRI) had performed it. Garziev et al. were able to show that interpreting mpMRI of the prostate has a learning curve that directly influences the performance of the targeted biopsy [78]. Another aspect is the inter-reader variability for the rating of suspicious lesions on mpMRI. A study comparing PI-RADS rated lesions to radical prostatectomy specimens, stated that inter-reader agreement was only 41% [79]. Another study by Schimmöller et al. showed that the inter-reader agreement for PI-RADS was "good" for cancer suspicious lesions and "moderate" for benign lesions with varying reader agreement depending on the mpMRI sequence (T2, DWI or DCE) [80]. Bratan et al. compared the independent mpMRI readings of two radiologists with the radical prostatectomy specimen. The study showed that PCa characteristics (GS and lesion size) influenced cancer detection, but the analysis also observed false positive ratings in 40% of the lesions [45]. Despite these discrepancies, mpMRI was still able to detect the index lesion. In order to improve the reader agreement of the mpMRI rating, the updated PI-RADS Version 2 included a categorical rating system as opposed to the sum score of PI-RADS Version 1. A recent analysis on the agreement of PI-RADS version 2 in a small cohort of 34 patients showed that the scoring of the index lesion were in accordance in 85%, but was 58% for the scoring of all lesions found on mpMRI [81]. The rating system changed from a sum score of the different MRI sequences to a categorical system. Obviously, this may result in different PI-RADS scores according to the PI-RADS version applied [82]. A study in 50 men comparing both PI-RADS versions concluded that PI-RADS version 2 had a "lower diagnostic accuracy" than the primary version [83]. Further analysis in larger cohorts will have to show what improvements need to made in order for future changes in the PI-RADS rating system to reduce the reader variability.

Another finding of our analysis was, that additional PCa lesions were only detected by the systematic biopsy, which even when unblinded to the histological results could not be assigned to a lesion on mpMRI. Although 67% of these lesions were GS 3+3, 18% of GS 3+4 and a few high risk cancers were not picked up by the mpMRI. This finding is in line with the data published by Radtke et al. where 86% of the insignificant non-index lesions where missed by mpMRI [84]. From our study, we concluded that when

performing a targeted biopsy, a negative targeted biopsy may be explained by a failure of the image fusion or a false rating of the PI-RADS lesion [61]. We therefore recommend maintaining a systematic biopsy in addition to the targeted biopsy protocol.

Value of an additional sagittal image fusion

The findings of our targeted biopsy failure study and the possibility of a false image fusion of MRI and US led to an analysis of how to improve the image fusion on a sensor-based fusion platform. The standard image fusion is performed in the axial plane for both the mpMRI and the real time US image [60]. Once the images are fused, the angulation of the US probe towards the base of the prostate is transformed to the MRI images by the platforms software. Nonetheless, especially ventral or basal lesions may need manual adjustment of the angle of the MRI image. From January 2015 on, the standard fusion protocol was updated to incorporate an image fusion in the sagittal plane, without increasing the total number of targeted cores. After marking the target lesion a three-point image fusion (bladder neck/prostatic base, apex and prostatic semi vesical angle) was performed in sagittal orientation. In order to evaluate the possible benefit of an added sagittal image fusion, our analysis included two groups of men. The group A had received an axial image fusion targeted biopsy in combination with a systematic biopsy from July 2013 to December 2014 and the group B had received a targeted biopsy in axial and sagittal image fusion in combination with a systematic biopsy as of December 2014 to September 2015. In the second group the addition of the sagittal image fusion did not increase in total number of biopsy cores. The overall cancer detection rates differed significantly between the two groups (group A 72% vs group B 85%). The difference may have been influenced by a higher rate of men with suspicious digital rectal examination, a higher rate of primary biopsies and a lower proportion of PI-RADS 3 lesions in group B, but the discrepancies remained when only men with negative digital rectal examination or only men with previously negative biopsies were analyzed. The multivariate analysis showed that “the additional sagittal image fusion was a significant predictor” for the detection of cancer in the targeted biopsy [85]. The proportion of cancers with a GS ≥ 7 that were missed by the targeted biopsy was 33% in group A vs. 9% in group B. On the one hand, the subgroup analysis of group B showed that biopsies taken after a sagittal image fusion alone had a lower

cancer detection than after axial image fusion (56% vs. 66%). On the other hand, the addition of the sagittal fusion to the targeted biopsies lead to an overall cancer detection rate of 76%, found 9 cases (13%) where the cancer would have been missed and lead to a Gleason upgrading in 10 cases (19%). Therefore adding the sagittal image fusion to the fusion biopsy protocol in a sensor-based setting improved the diagnostic accuracy of the procedure without increasing the total number of targeted biopsies. In regard to a axial or sagittal biopsy approach while performing an 3-D organ based MRI/US fusion biopsy, Hong et al. published similar findings of an improved detection of relevant PCa by the supplemental sagittal biopsy [86]. However, while in the 3-D organ based image fusion, the software of the biopsy platform fuses the calculated prostate volumes of the MRI images and the US images, the sensor based image fusion relies more on the accuracy of co-registration the axial image section of the T2-weighted sequence. On our biopsy platform the real-time US image, which usually does not match precise axial sections of the MRI, for the axial image fusion and biopsy the angulation of the MRI image needs to be manually adjusted to match the plane of the US image. This may present a potential source for inaccuracy of the image fusion. On the additional sagittal image fusion on our platform, three identical anatomical points (bladder neck, apical urethra and prostate semi vesical angle) are marked and co-registered by the platforms software in the sagittal plane of both the MRI and US images and therefore no manual adjustment of the angulation is necessary.

In a recently published study three different fusion biopsy platforms (Artemis^{TM}, Hitachi RVS and transperineal rigid image fusion) were compared ex vivo regarding targeting precision [77]. The overall detection rates of the biopsies taken in 18 phantoms were comparable for all three systems. The biopsy accuracy of the Hitachi RVS (the system used in our studies) was inferior compared to the other biopsy platforms in lesions of 5mm of size, whereas for lesions with 10mm the detection with the Hitachi RVS was 100%. Concerning the deviation of the targeted biopsy and the distance to the center of the lesion, the Hitachi platform showed a greater variability than the other tested systems. In the ex vivo study no sagittal image fusion was used for the sensor-based fusion. Nonetheless, in a clinical setting, the overall detection rates of our published data with the sensor-based rigid image fusion are comparable to the data generated on software driven organ-based fusion platforms [57-60, 87].

Besides the influence of the fusion in axial or sagittal orientation, the MRI lesion itself and the PI-RADS score present a significant influence on cancer detection by targeted biopsies [60, 88]. In the multivariate analysis of our study, the PI-RADS score was a significant predictor for the detection of PCa. The improved results in the group with axial and sagittal image fusion may have been influenced by the significant decrease regarding PI-RADS 3 rated lesions and the slight increase in PI-RADS 5 rated lesions. Additional potential factors affecting the biopsy outcome are a suspicious digital rectal examination and the number of men with a primary MRI/US fusion biopsy [58, 86, 88, 89]. In our uni- and multivariate analysis, the suspicious digital rectal examination was a significant predictor, whereas receiving a primary fusion biopsy was not. The group B (with sagittal fusion) had a higher rate of men with suspicious digital rectal examinations, but the higher cancer detection rate remained when only men with negative digital rectal examinations were analyzed. The same result was seen for the analysis excluding biopsy naïve men.

Besides the potential confounders, on the univariate and multivariate analysis, the additional sagittal image fusion persisted as an independent indicator for cancer detection in the targeted biopsy. Based on our analysis, we concluded that the addition of a sagittal image fusion to the classic axial image fusion increased the exactness of the sensor-based MRI/US fusion approach.

Sole MRI/US fusion targeted biopsy

The target lesion detected on the mpMRI is usually biopsied two to four times in order to enhance the diagnostic accuracy [58-60]. Radtke et al. published a comparison of the lesions detected in the mpMRI to the whole mount specimen after radical prostatectomy [84]. Overall, the mpMRI detected 92% of the index lesions, defined as “lesion with extraprostatic extension, the highest GS, or the largest tumor volume” [84]. The targeted biopsies alone would have detected 80% of the index lesions and adding a saturation biopsy lead to detecting 96% of the index lesions. In a recent review by Fütterer et al. focusing on the detection of clinically significant PCa with mpMRI, the negative predictive value for men without significant PCa ranged from 63% to 98% [90]. Based on this data many authors, including us, have suggested performing targeted biopsies in combination with a systematic biopsy, although this comes at the expense of a higher rate of GS 6 cancers [59, 60, 84]. The concept of a targeted-only approach

was evaluated in a study published by Baco et al. [91]. The randomized controlled trial included 175 biopsy naïve men who either received a targeted biopsy (median 2 cores; range 1-4 cores per target) in combination with a 12 core systematic biopsy or a the standard 12 core systematic biopsy. The cancer detection rates for significant cancer (defined as GS6 >5mm) of the targeted biopsies alone were comparable to the men who received only the standard 12-core systematic biopsy (overall 38% vs. 49% p-value 0.2). The detection rates were also comparable in the subgroup of men with normal digital rectal examination (targeted biopsy 21% vs. random biopsy 25%). Unfortunately, the detection rates for the combination of the targeted biopsies and the systematic biopsies were not stated.

The proposed strategies (targeted only or combination of targeted with systematic biopsies) therefore present an obvious disparity of what the urological community wants to achieve [84, 91]. Either to achieve similar results compared to the gold standard (TRUS guided systematic biopsy) with a dramatically reduced number of targeted biopsy cores or improve the cancer detection rate of the gold standard by adding the targeted biopsy regimen.

The answer may be strongly debatable and the results presented by Baco et al. might not be conferrable into the repeat biopsy setting. We therefore proposed a solution that is betwixt and in between. We retrospectively analyzed a cohort of men who had undergone MRI/US fusion biopsy in combination with a systematic biopsy regarding clinical parameters predicting an improved or equal outcome of a sole targeted biopsy compared to the combination [92]. The overall detection rates were comparable (targeted biopsies 63% vs. systematic biopsy 70%) and the same applied for the detection of the PCa risk group as defined by Siddiqui et al. [87]. In our series. A median of three targeted biopsies were taken, leading to 50% cancer detection in relation to the total number of targeted biopsies. In the systematic biopsy, 22% of the total number of biopsy cores were positive. A sole targeted biopsy approach would have missed 19% of all cancers and 7% of PCa with a GS ≥ 7. The published rate of significant PCa missed by the targeted biopsy ranges from 4-12% and our results are in line with this data [58, 59, 70, 84].

The uni- and multivariate analysis revealed three parameters predicting the identical or even improved cancer detection of a sole targeted biopsy approach: the maximal lesion

diameter on the mpMRI, the free/total PSA ratio and a suspicious digital rectal examination [92].

Choosing only the lesion diameter ≥12mm as a decision-aid for a sole targeted biopsy would have resulted in reducing the biopsy burden of 137 patients by 1370 biopsy cores, but overlooking 2% of high risk PCa and underestimating the PCa risk group in 12% on patients [92]. Other studies also concluded that the lesion size on mpMRI influenced the detection of clinically significant cancer [47, 59, 93]. The lesion size has also been given a greater importance in the updated version of the PI-RADS scoring system, where a lesion size >15mm will lead to a PI-RADS score of 5 [49]. On the other scale, smaller lesions (diameter < 7mm) visible on mpMRI are commonly associated with benign histology or the detection of low-risk cancer [94]. According to a study by Rosenkrantz el al., the reading of a prostate mpMRI may vary up to 40% depending on the reader [95]. In addition, as shown by our own previous publication, there is the possibility of a failure of the fusion biopsy [61]. The recently published ex vivo study on three different fusion biopsy systems also showed the greatest accuracy in lesions of 10mm in size [77]. The lesion size may therefore present a simple but efficient tool for selecting the “right” candidate for a sole targeted biopsy.

The total/free PSA ratio presented the statistically most powerful tool in favor of the targeted biopsy approach. Compared to the other parameters more high risk PCa was missed (five cases) and nine cases had a risk group upgrade in the systematic biopsy. Overall, this approach would have saved 1340 biopsy cores in 134 men. Huang et al. published a nomogram incorporating the total/free PSA with the goal to reduce the number of biopsies needed to detect PCa with a systematic biopsy [96]. Another study described the correlation of a reduced total/free PSA ratio to increased cancer detection and a rising rate of significant tumors [97].

In the 49 men with an abnormal digital rectal examination, directing only targeted biopsies towards the lesion would have resulted in one missed intermediate and one high-risk tumor and the underestimation of four men, saving 490 biopsy cores in total. The men undergoing mpMRI often have had prior negative biopsies and therefore the total number of men with a suspicious digital rectal examination may be limited. In addition the Rotterdam branch of the ERSPC trial published data demonstrating that an initial positive digital rectal examination with a negative prostate biopsy did not

increase the risk of being diagnosed with PCa in following screening intervals [98]. However, our data and the data published by Radtke et al. showed that an abnormal digital rectal examination does increase the likelihood of the targeted biopsy to diagnose clinically significant PCa [58]. Nonetheless, the digital rectal examination as a selection tool may exclude a large proportion of men who would otherwise be suitable for a targeted only biopsy.

Selecting the combination of lesion size and free/total PSA ratio as parameters for a targeted only approach would have selected 70 out of 251 men. In these men a targeted only biopsy would have not detected two (4%) of high risk PCa and underestimated three (6%) men [92]. Adding all three predictors of our analysis would have resulted in selecting only 14 men out of the whole cohort.

The concept of only targeting a suspicious lesion on the mpMRI will always have the risk of false negative targeted biopsy or an underestimation of the cancer burden, since PCa is known for its multifocality. Further, many men (57-72%) will have invisible cancers on the mpMRI which are mostly GS 6 cancers, but some intermediate and high risk cancer patients would be missed by a targeted only approach [61, 84, 88, 99]. The current guidelines and risk stratification tools available are still based on the biopsy of the whole prostatic gland and a sole targeted biopsy is clearly not sensible in all men. Our retrospective data opens an opportunity to counsel patients who are opting for a sole biopsy of the suspicious lesion. For a wider implementation of a sole targeted biopsy, further randomized studies on the topic are needed.

When we initiated MRI /US fusion guided targeted biopsies at our institution in 2012, this seemed a promising new tool to improve the standard systematic biopsy. In only four years since then, the concept of targeted biopsy has come a long way. In the repeat biopsy setting mpMRI and fusion biopsies is becoming the new standard in many hospitals and will be recommended in the new updated German PCa guideline [100]. In the primary biopsy setting there is an ongoing discussion of the value of mpMRI and targeted biopsies and currently the TRUS guided systematic biopsy will remain the standard recommended by the guidelines. A recent prospective study presented at the ASCO 2016 meeting on the value of the mpMRI as an entry test for primary biopsy

showed a great improvement compared to the systematic biopsy [101]. A trend also seen in our data. The decision pro or con primary MRI/US fusion guided biopsy are both political and economic. Roij et al. published a model calculation on the cost effectiveness of the mpMRI pathway in 2014 suggesting equal long-term expenses with improved quality of life, when a minimization of overdiagnosis and following overtreatment are taken into account [102]. The next few years will show where the data will take us. In any case, the paradigm shift away from systematic sampling of the whole prostate towards targeting the tumor has begun.

4. Summary

PCa presents the most common cancer in men of the western world. In the past two decades, the diagnostics of PCa was defined by the PSA test and the TRUS guided systematic prostate biopsy. The primary TRUS guided biopsy reveals PCa in only about half the men. Men with a negative biopsy and further elevated PSA levels often undergo subsequent TRUS guided biopsies with further declining PCa detection rates. Historically, imaging of the prostate with MRI played no role in the diagnostics of PCa, but recently the paradigm has started to shift. Visualizing the cancer suspicious lesions within the prostate on the mpMRI allowed for MRI/US fusion guided targeted biopsies rather than systematic sampling. The mpMRI and targeted biopsy therefore presented an option to improve on the standard of care. The first study therefore analyzed the cancer detection rates for men undergoing a MRI/US fusion guided targeted biopsy in combination with a 10-core systematic biopsy. The analysis included 310 men with a suspicious lesion according to PI-RADS. The detection rate of the whole cohort was 51% and 62% of cancers were GS ≥ 7. In patients undergoing a primary biopsy cancer was detected in 75% and a GS ≥ 7 was diagnosed in 75% of the cases. In the repeat biopsy setting, the detection of PCa ranged from 44% for men with ≥ 3 negative to 54% for men with one negative systematic biopsy. The PI-RADS score of the target lesion was a significant predictor for GS ≥ 7 detection. We concluded that the combination of targeted biopsies with a systematic biopsy seem to advance the performance of the standard biopsy regimen. Furthermore, we established a need to evaluate the impact of the PI-RADS score on targeted biopsies. The second publication focused on correlating each single PI-RADS score with the cancers detected by of MRI/US fusion biopsy. The PI-RADS classification for the standardized reporting of mpMRI was published in 2012. Data on the actual value of the PI-RADS score at the time our study was scarce and with 408 included men, our study presented the largest PI-RADS based analysis. In 56% of men PCa was found and the detection rates regarding the number of previous prostate biopsy were further improved compared to the first analysis. Further, the analysis showed again that the detection of significant PCa stayed constant independent of the number of prior biopsies (76-79%). Whereas men with PI-RADS 3 lesions had cancer in 26% of cases, men with PI-RADS 5 lesions were diagnosed with PCa in 89%. The study showed the strong correlation of the PI-RADS score to the detection of clinically relevant PCa. Nonetheless, we also recommend combining targeted biopsies with systematic biopsies for increased diagnostic accuracy.

The data of the cancers missed by targeted biopsy and detected by the systematic biopsy raised the question of the underlying reasons. The retrospective analysis included 61 men in which a blinded re-evaluation of each PI-RADS score was

performed. This was followed by an unblinded correlation of the mpMRI targets and the biopsy outcome and documentation of the reasons targeted biopsy failure. In 50% of the 90 evaluated lesions the re-reading lead to a downgrading of the initial PI-RADS score, which would have not indicated a targeted biopsy. In 40% of the lesions, the site of the cancer detected by systematic biopsy could clearly be linked to the suspicious mpMRI lesion, indicating a miss of the targeted biopsy. Interestingly, these lesions were mostly PI-RADS 4 or 5 and had a GS ≥ 7. The implications of the analysis was that adding the systematic biopsy will compensate for targeting errors and that “false high” mpMRI readings will affect the targeted biopsy outcome. The analysis of the targeted biopsy failures lead to the question if an additional image fusion in the sagittal plane would yield a diagnostic benefit. Of the 251 men included into the analysis, 89 men had an additional biopsy taken in sagittal image registration without increasing the total number of targeted biopsies. The analysis showed a significant correlation of the sagittal image fusion with a positive targeted biopsy result. The rate of significant PCa overlooked by the targeted biopsy was reduced by 8% by the supplemental sagittal image fusion and in nine men (10%), PCa was solely diagnosed on the sagittal targeted biopsy. Extending the standard MRI/US fusion protocol by a sagittal image fusion and sagittal targeted biopsy may improve the accuracy of a sensor-based MRI/US fusion guided targeted biopsy. Most published studies are based on the combination of targeted and systematic biopsies. The limitations of the targeted biopsy alone may be overcome by identifying the suitable patient rather than choosing a “one fits all” approach. We therefore retrospectively analyzed possible predictors for an equivalent or even superior outcome of a sole targeted biopsy compared to the systematic biopsy in regard to the PCa risk group. The analysis revealed that the lesion size >12mm, suspicious digital rectal examination and free/total PSA ratio were possible predictors for a sole targeted biopsy approach. Choosing the lesion size (137 men) as an entry test for a targeted only biopsy would have saved 1370 systematic biopsy cores, missing 11 low risk and two high risk PCa. Combining the lesion size with the total/free PSA ratio (70 men) would have reduced the biopsy burden by 700 cores, overlooking two high-risk PCa and underestimating the risk group in three men. Our data may be helpful in guiding patients inquiring the option of a targeted-only biopsy.

The mpMRI of the prostate and targeted biopsies have heavily changed the current approach of PCa diagnostics, but there is remaining room for improvement. Combining the mpMRI with biological markers, implementing positron emission tomography *(*PET)/MRI or developing MRI radionomics for increased data extraction, may further enhance the diagnostic accuracy and improve patient care.

5. References

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Acknowledgements

My greatest gratitude goes to Prof. Miller for giving me the opportunity to habilitate. I thank him for his scientific motivation and his great and continuous support.

I would like thank the following people for their support over the last years:

Prof. Bernd Hamm, PD Dr. Patrick Asbach and Dr. Matthias Haas for the great uro-radiologic collaboration, the intense discussions and their personal input throughout the last years.

PD Dr. Carsten Kempkensteffen, PD Dr. Stefan Hinz and Dr. Jörg Neymeyer for their clinical and scientific support.

Prof. Florian Fuller and Prof. Martin Schostak who gave me clinical and scientific support at the early stage of my urological career.

Dr. Karsten Günzel for his comradeship, the discussions and the work he put into our scientific projects.

PD Dr. Frank Friedersdorff for the discussions, motivation and collaboration.

Prof. Carsten Stephan and Dr. Andreas Maxeiner for their scientific motivation and input.

Dr. Ursula Steiner for her support throughout the years.

Dr. Hans Krause and his team for their support.

Dr. Bernd Timmermann, Dr. Stefan Börno, Prof. Michal Schweiger and the Core Sequencing Facility of the Max-Planck Institute for Molecular Genetics for their personal support, scientific input and the great time as a guest scientist.

All my current and past colleagues. Exemplary I want to name Dr. Katja Stier, Dr. Daniel Baumunk, Prof. Florian Jentzmik, PD. Dr. Jonas Busch, Chris Roller, Peter Werthemann, Prof. Steffen Weikert, Dr. John Buckendahl and Dr. Nils Krochmann.

My family, especially my wife Antonia Cash and my children without their backing and support none of this would have been possible.

Eidesstattliche Erklärung gemäß § 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

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Berlin, 05.01.2017 Dr. med. Hannes Cash