EUROPEAN UROLOGY ONCOLOGY XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?

Leonie Exterkate[a,*], *Olivier Wegelin*[b], *Jelle O. Barentsz*[c], *Marloes G. van der Leest*[c], *J. Alain Kummer*[d], *Willem Vreuls*[e], *Peter C. de Bruin*[d], *J.L.H. Ruud Bosch*[f], *Harm H.E. van Melick*[b,1], *Diederik M. Somford*[a,1]

[a] *Department of Urology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands;* [b] *Department of Urology, St. Antonius Hospital, Nieuwegein/Utrecht, The Netherlands;* [c] *Department of Radiology and Nuclear Medicine, Radboudumc Nijmegen, The Netherlands;* [d] *Department of Pathology, St. Antonius Hospital, Nieuwegein/Utrecht, The Netherlands;* [e] *Department of Pathology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands;* [f] *Department of Oncologic Urology, UMC, Utrecht, The Netherlands*

Article info

Article history:
Accepted June 5, 2019

Associate Editor:
Gianluca Giannarini

Keywords:
Diagnosis
Image-guided biopsy
Multiparametric magnetic resonance imaging
Prostatic neoplasms

Abstract

Background: The role of targeted prostate biopsies (TBs) in patients with cancer suspicious lesions on multiparametric magnetic resonance imaging (mpMRI) following negative systematic biopsies (SBs) is undebated. However, whether they should be combined with repeated SBs remains unclear.

Objective: To evaluate the value of repeated SBs in addition to TBs in patients with a prior negative SB and a persistent suspicion of prostate cancer (PCa).

Design, setting, and participants: A prospective study as part of a multicenter randomized controlled trial conducted between 2014 and 2017, including 665 men with a prior negative SB and a persistent suspicion of PCa (suspicious digital rectal examination and/or prostate-specific antigen >4.0 ng/ml).

Intervention: All patients underwent 3 T mpMRI according to Prostate Imaging Reporting and Data System (PI-RADS) v2. Patients with PI-RADS ≥3 were randomized 1:1:1 for three TB techniques: MRI-TRUS fusion TB (FUS-TB), cognitive registration fusion TB (COG-TB), or in-bore MRI TB. FUS-TB and COG-TB were combined with repeated SBs.

Outcome measurements and statistical analysis: Clinically significant prostate cancer (csPCa) was defined as Gleason ≥3 + 4. Differences in detection rates of csPCa, clinically insignificant PCa (cisPCa), and overall PCa between TBs (FUS-TB and COG-TB) and repeated SBs were compared using McNemar's test.

Results and limitations: In the 152 patients who underwent both TB and SB, PCa was detected by TB in 47% and by SB in 32% ($p < 0.001$, 95% confidence interval [CI]: 6.0–22%). TB detected significantly more csPCa than SB (32% vs 16%; $p < 0.001$, 95% CI: 11–25%). Clinically significant PCa was missed by TB in 1.3% (2/152). Combining

[1] These authors contributed equally to this work.
* Corresponding author. Department of Urology, Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, Nijmegen 6532 SZ, Gelderland, The Netherlands. Tel.: +31 24 365 82 55; Fax: +31 24 365 80 97.
E-mail address: l.exterkate@cwz.nl (L. Exterkate).

https://doi.org/10.1016/j.euo.2019.06.005

SB and TB resulted in detection rate differences of 6.0% for PCa, 5.0% for cisPCa, and 1.0% for csPCa compared with TB alone.

Conclusions: In case of a persistent suspicion of PCa following a negative SB, TB detected significantly more csPCa cases than SB. The additional value of SB was limited, and only 1.3% of csPCa would have been missed when SB had been omitted.

Patient summary: We evaluated the role of systematic biopsies and magnetic resonance imaging (MRI)-targeted biopsies for the diagnosis of prostate cancer in patients with prior negative systematic biopsies. MRI-targeted biopsies perform better in detecting prostate cancer in these patients. The value of repeated systematic biopsies is limited.

1. Introduction

The most commonly used technique for prostate cancer (PCa) detection is transrectal ultrasound (TRUS)-guided systematic biopsy (SB). SB is notorious for both underdiagnosing clinically significant prostate cancer (csPCa) due to undersampling of the anterior, midline, and apical regions of the prostate, and overdiagnosing clinically insignificant cancer (cisPCa) [1]. Many men undergo repeated SBs due to a persistent suspicion of PCa, which is associated with pain, anxiety, and a risk of infection [2–4].

Multiparametric magnetic resonance imaging (mpMRI) offers increased sensitivity for csPCa and localization accuracy of cancer suspicious regions (CSRs) [5]. Guidelines advise to perform mpMRI in patients with a prior negative SB and a persistent clinical suspicion of PCa [6,7]. CSRs on mpMRI enable MR-targeted biopsies (TBs). Systematic reviews of the literature have shown higher csPCa detection rates by TB than by SB, and a lower yield of cisPCa while requiring fewer biopsy cores [8–11]. Therefore, a combination of TB and SB is recommended. However, individual studies show heterogeneous results and are mainly focused on biopsy-naive men. Whether concurrent SBs are also warranted in a repeat biopsy setting is still unclear [7].

To evaluate the value of adding SB to TB in men with a negative prior SB and a persisting clinical suspicion of PCa, we compared detection rates of overall PCa, cisPCa, and csPCa between SB and TB.

2. Patients and methods

2.1. Study design

We performed a prospective predefined analysis of participants of the FUTURE trial, which was designed as a multicenter randomized controlled trial comparing three techniques of TB in patients with a persistent suspicion of PCa following a negative SB [12]. A detection difference between TBs and repeated SBs was defined as a secondary endpoint in the study protocol. Institutional review board approval was granted. The protocol was registered in the Dutch Trial Registry (NTR4988). All patients provided written informed consent. Between December 2014 and November 2017, men with a prior negative SB within the last 4 yr (eight or more cores from the peripheral zone) and a persistent suspicion of PCa (prostate-specific antigen [PSA] $\geq$4.0 ng/ml and/or suspicious digital rectal examination) were enrolled into two nonacademic centers of excellence for PCa diagnosis. Participants of the FUTURE trial who underwent both TB and SB were included in the current analysis.

Exclusion criteria for enrolment in the trial were prior diagnosed PCa, prior TB, proven urinary tract infection, contraindication for mpMRI or TB, imaging or TB or SB not performed according to protocol, or withdrawal of consent.

2.2. Multiparametric MRI

All patients underwent 3 T mpMRI according to the Prostate Imaging Reporting and Data System (PI-RADS) v2 (Supplementary Tables 1 and 2) [13]. Sequences included T2-weighted images, diffusion-weighted images, and dynamic contrast-enhanced images. Images were centrally evaluated by one of two expert radiologists (20 and 5 yr of experience in prostate MRI, each performing 1500 cases/yr). Radiologists were not blinded to clinical data. A written mpMRI report incorporating marked images was provided. If imaging showed no CSR, patients entered biochemical follow-up.

2.3. Biopsy

Patients with PI-RADS $\geq$3 lesions were randomized 1:1:1 to undergo TB using transperineal MRI-ultrasound fusion (FUS-TB; Biopsee; Medcom, Darmstadt, Germany), transrectal cognitive registration fusion (COG-TB; BK Pro Focus/Hitachi Hi-Vision Preirus), or transrectal in-bore MRI (MRI-TB; DynaTRIM; Invivo, Gainesville, FL, USA) [12,14]. TBs were performed by expert trained PhD candidates and urologists. TB cores were taken first and potted separately. A minimum of two TB cores per CSR was required for adequate sampling. SBs were taken by the same operator who performed TBs by transrectal approach, in cases of COG-TB, or by transperineal approach, in case of FUS-TB. SBs were performed using a standardized template irrespective of CSR location. For MRI-TB, it was not feasible to perform concomitant SB since this would have meant an additional procedure [15]. Therefore, in these patients, SB was omitted for ethical reasons and this group of patients was excluded from this analysis. The number of SB cores was based on common practice at the time of trial design and was dependent on prostate volume. Undersampling of the anterior/transition zone by a prior negative SB was taken into account by including at least two anterior and two transition zone cores in the SB template, for example, volume $<$40 cc = eight biopsies (two anterior, two transition zone, and four peripheral zone), volume 40–60 cc = 10 biopsies (two anterior, two transition zone, and six peripheral zone), and volume $>$60 cc = 12 biopsies (two anterior, four transition zone, and six peripheral zone). Specimens were processed in accordance with International Society of Urological Pathology standards and evaluated by an experienced uropathologist per center (11, 17, and 10 yr of experience in PCa diagnosis) [16]. Gleason scores and maximum cancer core length were reported. Clinically significant PCa was defined as Gleason $\geq$3 + 4. Analysis using an alternative threshold of csPCa was included in Supplementary Table 3.

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

2.4. Statistical analysis

Primary outcome was cancer detection rates (CDRs) by SB and TB. Secondary outcomes were csPCa and cisPCa detection rates. Subanalyses of CDRs per biopsy core, per approach (transperineal vs transrectal), and stratified per PI-RADS score were performed. Patient characteristics were summarized using mean ± standard deviation, or median and interquartile range as appropriate. To assess comparability between paired continuous variables, Wilcoxon signed-rank test was applied. McNemar's test was used to compare paired nominal data (CDRs of SB and TB) by means of absolute rate differences. CDRs of different TB techniques and different approaches were combined based on previously published data, which have shown comparable detection rates for different SB and TB [12,17,18].

Since there is no gold standard for prostate biopsies, we used (dis) concordance of results to calculate sensitivity and specificity as previously described [10]. A positive reference was defined as a positive test result on either test (SB or TB), that is, the number of concordant positive tests plus the number of discordant positive tests. Sensitivity of TB and SB was calculated as the number of positive results on either TB or SB divided by the total number of positive tests (TB and SB combined). Specificity was calculated as the number of negative results on either SB or TB divided by the total number of negative tests. The relative sensitivity or relative specificity is the sensitivity or specificity ratio between TB and SB.

Statistical analyses were performed using SPSS v24 (SPSS Inc., Chicago, IL, USA) and 5% significance levels were adopted in all tests. The trial was not primarily powered for the comparison of TB and SB, as it was a predefined secondary endpoint. For further details regarding sample size calculation of the trial, we refer to our previously published work [12].

3. Results

3.1. Patients

A total of 695 men were recruited in the trial and 665 men were included in the final analysis (Fig. 1). A total of 234 (35%) patients with a PI-RADS ≥3 lesion on mpMRI were randomized for TB: 79 for FUS-TB, 78 for COG-TB, and 77 for MRI-TB. In all, 152 patients underwent both TB (76 COG-TB and 76 FUS-TB) and SB. Table 1 shows baseline characteristics of study populations. In the analyzed cohort that underwent both TB and SB, mean age was 66 ± 6.7 yr, mean prebiopsy PSA was 11 ± 7.9 ng/ml, and mean PSA density (PSAD) was 0.23 ± 0.16 ng/ml/ml. By combining SB and TB, the overall CDR was 53% (81/152), csPCa was detected in 35% (53/152), and cisPCa was detected in 18% (28/152).

3.2. Comparison of CDR by SB and TB

Crosstabs compare PCa detection rates of SB and TB (Table 2). CDRs for overall PCa were 47% (71/152) by TB and 32% (49/152) by SB. The 15% difference (95% confidence interval [CI]: 6.0–22%) was significant ($p < 0.001$). The overall CDR by combining SB and TB was 53%, representing a PCa detection rate difference of 6.0% compared with TB alone (CDR of 47%).

Sensitivity for overall PCa was 0.88 for TB and 0.60 for SB, with relative TB/SB sensitivity of 1.5. Specificity for overall PCa was 0.72 for TB and 0.91 for SB, with relative TB/SB specificity of 0.80.

Clinically significant PCa was detected by TB in 34% (51/152) and by SB in 16% (24/152). The 18% difference in the detection rate (95% CI: 11–25%) was significant ($p < 0.001$). The combination of SB and TB detected csPCa in 35% (53/152) cases, representing a csPCa detection rate difference of 1.0% compared with TB alone (34% csPCa). Sensitivity of csPCa was 0.96 for TB and 0.45 for SB, with relative sensitivity of 2.1. Specificity of csPCa was 0.78 for TB and 0.98 for SB, with relative specificity of 0.80.

TB detected cisPCa in 13% (20/152) compared with 16% (25/152) by SB ($p = 0.4$, 95% CI:–4.0% to10%). The combination of SB and TB detected cisPCa in 18% (28/152) cases, representing a cisPCa detection rate difference of 5.0% compared with TB alone (13% cisPCa).

In patients in whom SB did not detect PCa, TB detected PCa in 21% and csPCa in 13%. Alternatively, in patients in whom TB did not detect PCa, SB detected PCa in 6.6% and csPCa in 1.3%. Overall, csPCa was missed by TB in 1.3% and by SB in 19%. This 18% difference (95% CI: 11–to 24%) was significant ($p < 0.001$). Relative to the group of detected csPCa ($n = 53$), TB missed 3.8% of csPCa and SB missed 55% csPCa. SB detected cisPCa in 5.3% of patients in whom TB detected no PCa, and TB detected cisPCa in 7.9% of patients in whom SB detected no PCa. See Supplementary Table 3 for outcomes for alternative csPCa thresholds.

A significantly higher number of TB cores were positive for PCa (34%, 201/593) than SB cores (17%, 100/1533; $p < 0.001$, 95% CI: 23–32%), resulting in a lower number of cores (median 3 vs 10 cores per individual) needed to achieve a higher CDR (Table 3). A subanalysis of CDRs stratified per PI-RADS score (Supplementary Table 4) and per biopsy approach (transrectal vs transperineal; Supplementary Table 5) did not show significant differences.

3.3. Radical prostatectomy

A radical prostatectomy (RP) was performed in 40 patients with a CSR on mpMRI. Of these 40 patients, 38 were diagnosed with PCa by at least one TB and 19 were diagnosed by at least one SB. Seventeen patients were diagnosed with PCa by both TB and SB. Gleason grading according to Epstein of TB cores and RP specimens was concordant in 17 of 38 (45%) patients, upgraded in seven of 38 (18%) patients, and downgraded in 14 of 38 (37%) patients. In three of seven (43%) upgraded cases, it concerned an upgrade from cisPCa to csPCa. Gleason grading of SB and RP specimens was concordant in six of 19 (32%) patients, upgraded in six of 19 (32%) patients, and downgraded in seven of 19 (37%) patients. In six of six (100%) upgraded cases, it concerned an upgrade from cisPCa to csPCa.

4. Discussion

4.1. Main findings

To prevent cisPCa overdiagnosis and overtreatment without missing out on csPCa, there is an obvious need for an optimal imaging and biopsy approach in men with a prior

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

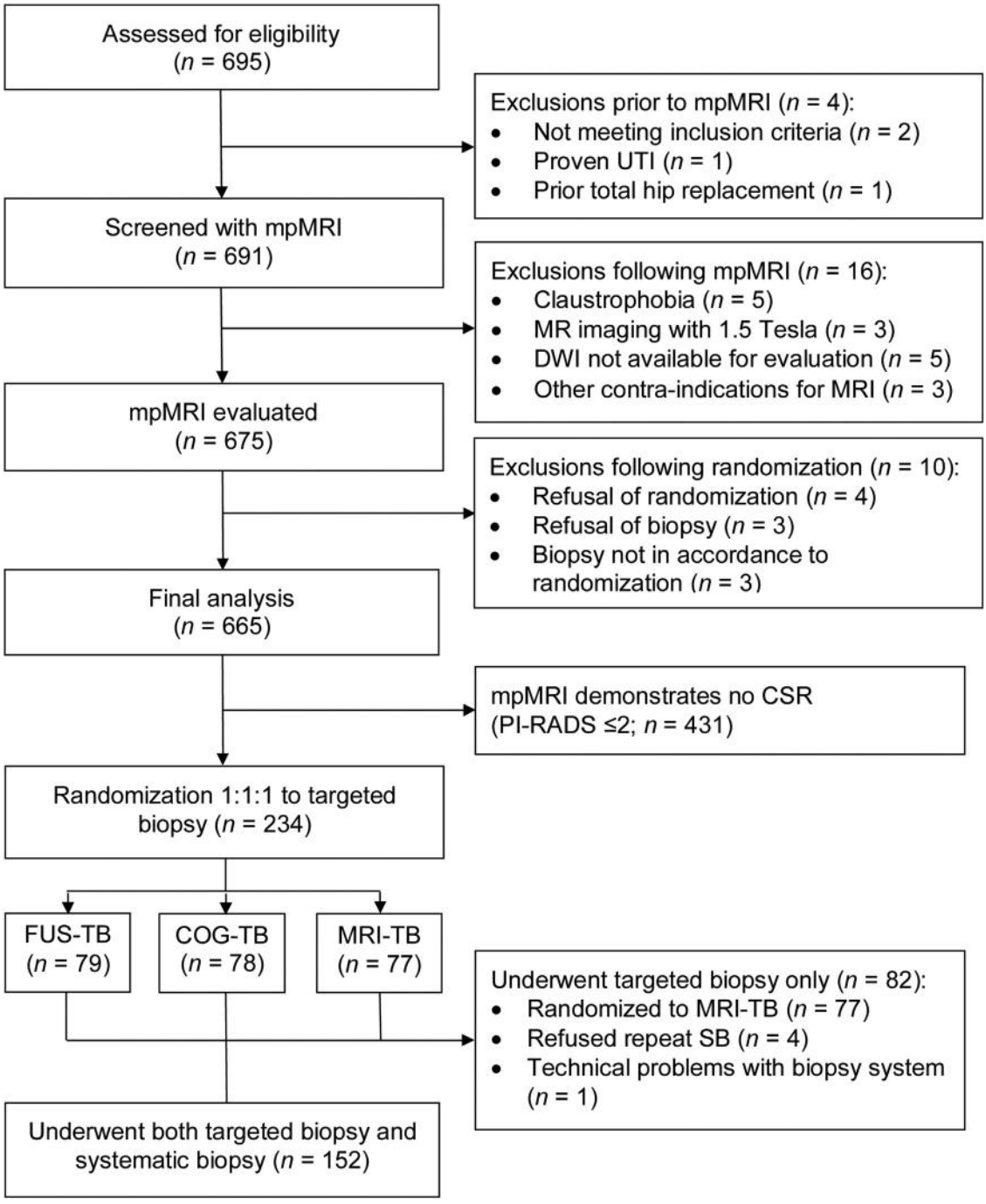

Fig. 1 – Flowchart of the study. COG-TB = cognitive registration targeted biopsy; CSR = cancer suspicious region; DWI = diffusion weighted imaging; FUS-TB = MRI-TRUS fusion targeted biopsy; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI targeted biopsy; PI-RADS = Prostate Imaging Reporting and Data System; SB = systematic biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection.

negative SB and a persistent clinical suspicion of PCa. The aim of this analysis was to evaluate the value of adding SB to TB in a homogeneous cohort of men with a prior negative SB and a persistent suspicion of PCa.

In this prospective cohort, as part of a randomized controlled trial, TB significantly increased CDR of overall PCa as well as csPCa compared with SB. The number of biopsy cores needed to achieve a higher CDR was significantly lower for TB than for SB. The additional value of repeated SBs was limited. Using TB, only few csPCa cases were missed and fewer cisPCa cases were detected compared with SB.

4.2. Current knowledge

Recently, a Cochrane review and meta-analysis and the updated European Association of Urology (EAU) guideline

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

Table 1 – Study population characteristics.

	Cohort that underwent SB + TB (*n* = 152)
Age (yr), mean (SD)	66 (6.7)
PSA (ng/ml), mean (SD)	11 (7.9)
Volume TRUS (ml), mean (SD)	47 (16)
PSAD (ng/ml/ml), mean (SD)	0.23 (0.16)
Clinical stage (DRE), *n* (%)	
cT1c	122 (80)
cT2a/b	27 (18)
cT2c	2 (1.3)
cT3a	1 (0.66)
Number of prior negative biopsy procedures (*n*), median (IQR)	1 (1–2)
Time interval from previous biopsy to mpMRI (mo), median (IQR)	8 (4–24)
Time interval from mpMRI to biopsies (d), median (IQR)	40 (26–56)
PI-RADS score, *n* (%)	
3	42 (28)
4	63 (41)
5	47 (31)
CSRs per patient (*n*), median (IQR)	1 (1–1)
CSR location, *n* (%)	
Anterior	59 (40)
Midline	14 (9.2)
Posterior	79 (52)
Overall PCa detection rate, *n* (%)	81 (53)
Overall csPCa detection rate, *n* (%)	53 (35)

csPCa = clinically significant prostate cancer (Gleason ≥3 + 4); CSR = cancer suspicious region; DRE = digital rectal examination; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; SB = systematic biopsy; SD = standard deviation; TB = targeted biopsy; TRUS = transrectal ultrasound.

Table 2 – Biopsy outcomes.

	Systematic biopsy			Total
	No PCa	cisPCa	csPCa	
Targeted biopsy				
No PCa	71 (47%)	8 (5.3%)	2 (1.3%)	81
cisPCa	12 (7.9%)	8 (5.3%)	0 (0.0%)	20
csPCa	20 (13%)	9 (5.9%)	22 (14%)	51
Total	103	25	24	*n* = 152

cisPCa = clinically insignificant prostate cancer (Gleason 3 + 3); csPCa = clinically significant prostate cancer (Gleason ≥3 + 4); PCa = prostate cancer.

recommend to perform TB only when mpMRI is positive in the repeated biopsy setting [19,20]. However, the evidence regarding this recommendation is still weak, as rated by the EAU Guideline Committee. Although the research question of our study might not be novel, the results are of clinical relevance. We performed an analysis of a predefined secondary endpoint within a randomized controlled trial. This has resulted in protocoled high-quality data collection and management of a homogeneous cohort of patients in centers of excellence regarding PCa diagnosis. Therefore, our results contribute to increase the level of evidence for the guideline recommendation on TB and SB in the repeat biopsy setting.

Table 3 – Biopsy cores.

	TB cores	SB cores
Total cores	593	1533
Per subject, *n* (median, IQR)	3 (3–4)	10 (8–12)
PCa positive cores	201	100
Positivity rate (%)	34	6.5

IQR = interquartile range; PCa = prostate cancer; SB = systematic biopsy; TB = targeted biopsy.

So far, several studies have compared CDRs of SB and TB in patients with a prior negative SB, and found csPCa detection rates by TB to range from 15% to 48% depending on patient selection, imaging quality, TB technique used, and applied definition of csPCa [21–24]. In these studies, repeated SB yields of csPCa ranged from 9.0% to 31%. The authors of these papers concluded that addition of SB may be needed to avoid missing csPCa. The results from this current study seem to contradict these conclusions.

In accordance with our findings, a systematic review and meta-analysis by Schoots et al. [10] showed that TB detected significantly more (cs)PCa than SB (relative sensitivity of 1.54 [95% CI: 1.05–2.57]) in a subgroup of men with a prior negative SB. The authors did not formulate a recommendation regarding the value of repeated SBs in these men, possibly due to the heterogeneity of the study populations. On the contrary, Mischinger et al. [15] recently evaluated the performance of transperineal robot-assisted TB compared with SB in primary and repeat biopsy settings, and found that TB and SB showed similar csPCa detection rates. However, their patient selection was not restricted to fixed PI-RADS thresholds, and more importantly a heterogeneous population was studied. Despite the high sensitivity of TB for csPCa, as presented by Filson et al. [25] in a recent prospective trial, concerns regarding missing csPCa may arise when omitting SB in the repeat biopsy setting. In the repeat biopsy setting, studies show variable percentages of missed csPCa by TB ranging from 0.0% to 23% [23,24,26,27]. Filson et al. [25] showed in a mixed population (biopsy naive, with a prior negative SB, and under active surveillance) of men with PI-RADS ≥3 that a combination of TB and SB (*n* = 289) detected more cases of csPCa in men than either modality alone (229 by TB and 199 by SB). Interestingly, a recent study showing frequent overlap of SB and TB cores further supports our findings that SB adds limited diagnostic improvement in a repeat biopsy setting [28].

In our study, the combination of SB and TB resulted in similar csPCa detection to TB alone (35% vs 34%, respectively). TB missed csPCa in only 1.3% of patients, indicating that SB could have been safely omitted in this group of patients. In one case, it concerned a sampling error (a positive SB in the same quadrant as a suspicious lesion on mpMRI); in the other, the lesion was not diagnosed on mpMRI.

The correlation between TB and final RP specimen has not been studied widely. However, in concordance with our findings, previous studies have shown that Gleason grading is often underestimated by SB (upgrading on prostatectomy between 30% and 43%) due to a large

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

sampling error [29–32]. Discrepancy may lead to undertreatment as an upgrade from cisPCa to csPCa is commonly seen. We found less upgrading from cisPCa to csPCa after TB than after SB, which may enhance therapeutic decision making. Our relatively low concordance rate between TB and RP specimens (45%) compared with most of the literature reports may be explained by our relatively low number of cores per CSR (median 3–4), which might have resulted in a sampling error. Furthermore, while most studies report on (mixed) cohorts of biopsy-naïve men, men with a previous negative biopsy, and men under active surveillance, we analyzed a homogeneous cohort of men with a previous negative biopsy. This repeat biopsy setting may have influenced our results by a higher incidence of smaller, harder-to-approach lesions, resulting in a subsequent sampling error and a lower concordance rate compared with other studies [33–38].

Nevertheless, some csPCa cases might fall below the threshold of mpMRI, and therefore, follow-up of men with negative mpMRI and TB, in whom clinical suspicion persists, is of great importance. Currently, our follow-up is limited in duration, and a more elaborate analysis on this issue will follow after completion of 2–5 yr of follow-up for all patients.

4.3. Limitations

This study has some limitations. First of all, the FUTURE trial was designed and powered to compare CDRs of three different TB techniques, and sample size calculations for our subgroup analyses are lacking. In this study, the same operator performed TB and SB, and therefore was not blinded to the CSR on mpMRI while performing SB. We attempted to limit this bias by using a standardized SB template based on prostate volume. In addition, CDRs for csPCa are dependent on the definition of csPCa. Therefore, CDRs need to be interpreted with caution, especially when tumor burden, PSA value, and clinical staging are not taken into account. We attempted to reduce this limitation by applying a secondary definition of csPCa incorporating tumor volume, PSAD, and clinical staging (Supplementary Table 3). Potentially TB samples CSR more thoroughly than SB, resulting in higher Gleason scores. This study uses earlier published definitions of csPCa based on random sampling. Consensus on the definition of csPCa in the TB era is urgently needed to compare between series. Lastly, we are not informed on the actual PCa prevalence in our cohort, as we used the combination of the two analyzed techniques as our gold standard. In our study, patients were enrolled in two nonacademic centers of excellence for PCa diagnosis. All mpMRI studies were performed following PI-RADS v2 standards and centrally reviewed in an academic center. Therefore, we believe that our results can be compared with other centers of excellence for PCa diagnosis (either academic or nonacademic), while on the contrary, generalizability of the presented outcomes to general practice may be limited. Nevertheless, this study shows how accurate mpMRI and consequent TB can be in an optimal situation. Therefore, our results are in agreement with the statement of Rosenkrantz et al. [7] that omission of SB should be considered only when quality of mpMRI acquisition and TB can be assured.

5. Conclusions

In men with a prior negative SB and a persistent suspicion of PCa, TBs have a 18% higher csPCa detection rate than SBs. The combination of SB and TB resulted in csPCa detection rate differences of 6.0% for PCa, 5.0% for cisPCa, and 1.0% for csPCa compared with TB alone. Only 1.3% csPCa would have been missed if SB had been omitted. Therefore, the value of adding SB to TB in a repeat biopsy setting is limited.

Author contributions: Leonie Exterkate had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wegelin, van Melick, Somford, Barentsz.
Acquisition of data: Exterkate, Wegelin, Somford, van Melick, Barentsz, van der Leest, Kummer, Vreuls, de Bruin.
Analysis and interpretation of data: Wegelin, Exterkate, Somford, van Melick, Barentsz, Bosch.
Drafting of the manuscript: Exterkate.
Critical revision of the manuscript for important intellectual content: Exterkate, Wegelin, Somford, van Melick, Barentsz, Bosch, van der Leest, Kummer, Vreuls, de Bruin.
Statistical analysis: Exterkate, Wegelin.
Obtaining funding: Wegelin, van Melick, Somford.
Administrative, technical, or material support: Exterkate, Wegelin.
Supervision: Somford, van Melick, Barentsz, Bosch.
Other: Statistical analysis was performed with the help of Dr. J.C. Kelder (see the Acknowledgments section).

Financial disclosures: Leonie Exterkate certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This investigation was sponsored by the St. Antonius Hospital Research and Innovation Funds, Foundation Urology 1973, and Astellas Pharma.

Acknowledgments: We would like to thank the following hospitals (in alphabetical order) for presenting eligible patients for recruitment: Beatrix Rivas Hospital Gorinchem, Bernhoven Hospital Uden, Canisius Wilhelmina Hospital Nijmegen, Diakonessenhuis Hospital Utrecht, Gelderse Vallei Hospital Ede, Gelre Hospital Apeldoorn/Zutphen, Rivierenland Hospital Tiel, Slingeland Hospital Doetinchem, St. Antonius Hospital Nieuwegein/Utrecht, St. Jansdal Hospital Harderwijk, Streekziekenhuis Koningin Beatrix Winterswijk, Zuwe Hofpoort Hospital Woerden. Furthermore, we would like to thank the urology, pathology, radiology, and research departments of our recruitment hospitals for their effort. We would also like to thank all men for their agreement and motivation to take part in this study. Statistical analysis was performed with the help of Dr. J.C. Kelder (Department of Epidemiology and Statistics, St. Antonius Hospital, Nieuwegein/Utrecht).

Acknowledgments: We are grateful to our patients and their families. We also thank the investigators, nurses, statistical team, and research staff for their dedication to this project.

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2019.06.005.

References

[1] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[2] Liss MA, Ehdaie B, Loeb S, et al. An update of the American Urological Association white paper on the prevention and treatment of the more common complications related to prostate biopsy. J Urol 2017;198:329–34.
[3] Welch HG, Fisher ES, Gottlieb DJ, Barry MJ. Detection of prostate cancer via biopsy in the Medicare-SEER population during the PSA era. J Natl Cancer Inst 2007;99:1395–400.
[4] Lujan M, Paez A, Santonja C, Pascual T, Fernandez I, Berenguer A. Prostate cancer detection and tumor characteristics in men with multiple biopsy sessions. Prostate Cancer Prostatic Dis 2004;7:238–42.
[5] Futterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015;68:1045–53.
[6] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[7] Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol 2016;196:1613–8.
[8] Wegelin O, van Melick HH, Hooft L, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol 2017;71:517–31.
[9] Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2015;68:8–19.
[10] Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438–50.
[11] Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22–9.
[12] Wegelin O, Exterkate L, van der Leest M, et al. The FUTURE trial: a multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. Eur Urol 2019;75:582–90.
[13] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40.
[14] Wegelin O, van Melick H, Somford D, van Basten J, Kummer J. The future trial: fusion target biopsy of the prostate using real-time ultrasound and MR images. A multicenter RCT on target biopsy techniques in the diagnosis of prostate cancer. J Clin Trials 2015;5:248. http://dx.doi.org/10.4172/2167-0870.1000248.
[15] Mischinger J, Kaufmann S, Russo GI, et al. Targeted vs systematic robot-assisted transperineal magnetic resonance imaging-transrectal ultrasonography fusion prostate biopsy. BJU Int 2018;121:791–8.
[16] Epstein JI, Allsbrook Jr WC, Amin MB, Egevad LL, IG Committee. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228–42.
[17] Takenaka A, Hara R, Ishimura T, et al. A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis 2008;11:134–8.
[18] Hara R, Jo Y, Fujii T, et al. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008;71:191–5.
[19] Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019;4:CD012663.
[20] Mottet N, Briers E, Cornford P, et al. EAU–ESTRO–ESUR–SIOG guidelines on prostate cancerPresented at the EAU Annual Congress Barcelona. 2019 https://uroweb.org/guideline/prostate-cancer/
[21] Mendhiratta N, Meng X, Rosenkrantz AB, et al. Prebiopsy MRI and MRI-ultrasound fusion-targeted prostate biopsy in men with previous negative biopsies: impact on repeat biopsy strategies. Urology 2015;86:1192–8.
[22] Salami SS, Ben-Levi E, Yaskiv O, et al. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU Int 2015;115:562–70.
[23] Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809–15.
[24] Vourganti S, Rastinehad A, Yerram N, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. J Urol 2012;188:2152–7.
[25] Filson CP, Natarajan S, Margolis DJ, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer 2016;122:884–92.
[26] Arsov C, Rabenalt R, Blondin D, et al. Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. Eur Urol 2015;68:713–20.
[27] Tewes S, Hueper K, Hartung D, et al. Targeted MRI/TRUS fusion-guided biopsy in men with previous prostate biopsies using a novel registration software and multiparametric MRI PI-RADS scores: first results. World J Urol 2015;33:1707–14.
[28] Patel N, Cricco-Lizza E, Kasabwala K, et al. The role of systematic and targeted biopsies in light of overlap on magnetic resonance imaging ultrasound fusion biopsy. Eur Urol Oncol 2018;1:263–7.
[29] Milonas D, Grybas A, Auskalnis S, et al. Factors predicting Gleason score 6 upgrading after radical prostatectomy. Cent Eur J Urol 2011;64:205–8.
[30] King CR. Patterns of prostate cancer biopsy grading: trends and clinical implications. Int J Cancer 2000;90:305–11.
[31] Suer E, Gokce MI, Gulpinar O, et al. How significant is upgrade in Gleason score between prostate biopsy and radical prostatectomy pathology while discussing less invasive treatment options? Scand J Urol 2014;48:177–82.

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005

[32] Cohen MS, Hanley RS, Kurteva T, et al. Comparing the Gleason prostate biopsy and Gleason prostatectomy grading system: the Lahey Clinic Medical Center experience and an international meta-analysis. Eur Urol 2008;54:371–81.
[33] Xu N, Wu YP, Li XD, et al. Risk of upgrading from prostate biopsy to radical prostatectomy pathology: is magnetic resonance imaging-guided biopsy more accurate? J Cancer 2018;9:3634–9.
[34] Porpiglia F, Passera DEL, et al. Multiparametric-magnetic resonance/ultrasound fusion targeted prostate biopsy improves agreement between biopsy and radical prostatectomy Gleason score. Anticancer Res 2016;36:4833–9.
[35] Lanz C, Cornud F, Beuvon F, et al. Gleason score determination with transrectal ultrasound-magnetic resonance imaging fusion guided prostate biopsies—are we gaining in accuracy? J Urol 2016;195:88–93.
[36] Baco E, Ukimura O, Rud E, et al. Magnetic resonance imaging-transrectal ultrasound image-fusion biopsies accurately characterize the index tumor: correlation with step-sectioned radical prostatectomy specimens in 135 patients. Eur Urol 2015;67:787–94.
[37] Borkowetz A, Platzek I, Toma M, et al. Direct comparison of multiparametric magnetic resonance imaging (MRI) results with final histopathology in patients with proven prostate cancer in MRI/ultrasonography-fusion biopsy. BJU Int 2016;118:213–20.
[38] Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol 2014;192:1367–73.

Please cite this article in press as: Exterkate L, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.06.005