Original research article

UJ Urologia Journal

Urologia Journal
2019, Vol. 86(1) 9–16

DOI: 10.1177/0391560319834490
journals.sagepub.com/home/urj
SAGE

MRI ultrasound fusion biopsy in prostate cancer detection: Are randomized clinical trials reproducible in everyday clinical practice?

Susanna Cattarino[1], Valerio Forte[2], Stefano Salciccia[1], Francesco Maria Drudi[2], Valerio Cantisani[2], Alessandro Sciarra[1], Andrea Fasulo[3] and Mauro Ciccariello[2]

Abstract

Introduction: The aim of this study was to evaluate the performance of multiparametric magnetic resonance imaging (mpMRI)–ultrasound (US) fusion-targeted biopsies (TB) in men with primary and repeated biopsies comparing the cancer detection rate (CDR) of random biopsies (RB) + TB versus only TB.

Methods: The present study is a real-life study on patients with primary and prior negative prostate biopsies with suspicious PCa. A total of 130 men with prostate-specific antigen (PSA) value >2.5 ng/dL and/or abnormal digital rectal examination (DRE) were included in the study and subjected to mpMRI. Patients with >2 previous biopsies and/or with $\geqslant 3$ suspected lesions on MRI and/or prostate imaging-reporting and data system (PIRADS) value $\geqslant 4$ (n:30 pts) were subjected only to TB on the areas indicated by mpMRI. All the other patients (n:70 pts) were subjected to standard random laterally directed 10-core plus TB on the areas indicated by mpMRI.

Results: The overall CDR was 53% (53/100). In relation to PIRADS score, the overall CDR was 0, 40% (12/30), 56.83% (29/51), and 84% (11/13) for PIRADS 2, 3, 4, and 5, respectively. According to biopsy modality, CDR for RB + TB was 50% (35/70) and CDR for TB was 60% (18/30) with a *p*-value of 0.3632.

Discussion: MRI–US fusion biopsy is associated with a high CDR of clinically significant PCa (csPCa). MRI–US fusion biopsy could be a reasonable approach in patients with previous negative biopsy and high PIRADS score on MRI, to ensure a high CDR of csPCa and to reduce the diagnosis of clinically insignificant tumors.

Keywords

Prostate cancer, multiparametric magnetic resonance, random biopsy, targeted biopsy, clinically significant tumor

Date received: 5 January 2018; accepted: 30 January 2019

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths in men.[1] According to the European Association guidelines,[2] the current standard method of diagnosing PCa remains transrectal ultrasound (TRUS)-guided prostate biopsy. It has been proven that approximately 30% of cases miss significant tumor detection.[3] Prostate biopsy protocols have therefore evolved over the years toward protocols that propose either to increase the number of biopsies, to combine new markers or to acquire a better visualization of the prostate with new imaging techniques, first of all the multiparametric magnetic resonance imaging (mpMRI) of the prostate. The association of T2-weighted with diffusion-weighted and dynamic contrast-enhanced (DCE) imaging has excellent sensitivity for

[1]Department of Urology, Sapienza University of Rome, Rome, Italy
[2]Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University of Rome, Rome, Italy
[3]ISTAT (Statistics Institute of Rome), Rome, Italy

Corresponding author:
Susanna Cattarino, Department of Urology, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy.
Email: susanna.cattarino@uniroma1.it

the detection and localization of PCa[4] so much that the most recent European and American Urological (EAU) Association recommends a 10–12 core systematic TRUS biopsy including a target biopsy (TB) of any mpMRI suspicious lesions during repeated biopsy.[2,5]

Several studies showed that mpMRI combined with MRI–ultrasound (US) fusion technology, which consists in merging previously captured MRI images with live TRUS images, is a promising method in the detection of PCa with high cancer detection rate (CDR) of >60%.[6,7] Early trials of TB included men with primary biopsy or with previous negative biopsies comparing CDR in random and targeted biopsies, especially in terms of clinically significant PCa (csPCa).[8,9] Some authors suggested that mpMRI–US fusion TB is superior to standard biopsy either in terms of capturing csPCa[10–12] or in terms of morbidity.

Today, this has led to a new important question for clinical practice: is a standard biopsy still necessary if a targeted one was also performed? Moreover, which is the optimal setting for patients who should be subjected to fusion biopsy? Considering these questions, the aim of this study was to prospectively evaluate the performance of mpMRI–US fusion targeted biopsies in men with primary and repeated biopsies comparing the CDR of RB + TB versus TB especially in terms of csPCa. The relationship of increasing number of previous biopsies and the CDR was also analyzed. We finally correlate CDR with the prostate imaging-reporting and data system (PIRADS) scoring system.

Materials and methods

Study design and population

The present study is a single-center study based on daily clinical practice. Patients at first or with previous negative prostate biopsies have been examined; their risk of having PCa was assessed by prostate-specific antigen (PSA) value and/or digital rectal examination (DRE). The study was conducted after receiving approval of the protocol from our institutional board committee of Policlinico Hospital and informed consent was obtained from all patients. Between September 2015 and March 2016, 130 men with PSA value >2.5 ng/dL and/or abnormal DRE visited outpatient clinic of the Department of Urological Sciences, Policlinico Umberto-I, were included in the study. Inclusion criteria were the following: age > 50 years, PSA > 2.5 ng/dL, at least one suspicious lesion on mpMRI, and signed informed consent. All patients were subjected to mpMRI (T2-weighted with diffusion-weighted and DCE imaging) in the Department of Radiology. A total of 30 men with no suspicious lesions on mpMRI were excluded from the protocol and were followed in urological daily outpatient clinics. A population of 100 patients was finally included in the study. Moreover, we divided the population into two non-randomized groups: patients with >2 previous biopsies and/or with ⩾3 suspected lesions on MRI and/or PIRADS value ⩾4 (n:30 pts) were subjected only to targeted biopsy (TB), using the areas depicted by mpMRI as landmarks. The other patients (n:70 pts) were subjected to the standard, laterally directed, random 10-core biopsy, including TB on the areas indicated by mpMRI. The mean number of samples per procedure was 6 for TB. In Table 1, characteristics of the population are summarized.

Multiparametric MRI

To evaluate the prostate gland, examinations were performed on a 3 T or 1,5 T magnets upon availability (MAGNETOM Avanto and Verio, Siemens Medical Solutions) equipped with a phased-array coil and an endorectal coil. The MRI protocol included the following sequences: T2-weighted (T2w) turbo spin-echo sequences (repetition time (TR), 4500 ms; echo time (TE) 110 ms; thickness, 3 mm; and matrix, 352 × 352) in axial, sagittal, and coronal planes. Diffusion-weighted imaging sequences: slice thickness, 3 mm; TR, 3100 ms; TE, 102 ms; and exponential *b* values of 0, 500, 1.000 s/mm^2 on the 1,5 T magnet. Additional *b* value of 2.000 s/mm^2 was performed on the 3 T magnet. DCE-MRI was obtained using a gradient-echoT1-weighted sequence in axial planes (TR, 3 ms; TE, 2 ms; thickness, 3 mm; time resolution, 12 sections/3 s; and matrix, 320 × 192). Collected data were reviewed by using PI—RADS v.2 classification system.

Prostate biopsy

MRI–US fusion technique uses software algorithms and dedicated hardware to overlay the data obtained from MRI and US examinations, delivering a greater accuracy of the prostate biopsy. The system used for this study is the Urostation (Koelis—Grenoble, France). The procedure involves the following steps. First, prostate gland needs to be outlined through axial T2 images where three key points must be set: prostate base, apex, and rear portion. This process allows the software to create a three-dimensional model of the gland where the operator proceeds to draw areas, which represent target lesions previously identified by MRI. Finally, the fusion process between MRI and US images takes place.

Biopsies were performed in dorsal lithotomy, with transrectal approach. A 18-G biopsy gun with a sample length of 18 mm was employed. In targeted biopsy, at least two cores per lesion were taken, depending on lesion size. In systematic biopsy, the needle was placed according to a 10-core custom scheme: two cores from the basal portion (lateral and paramedial), two from the midgland (lateral and paramedial), and one from the apex (on each side of the gland).

Table 1. Characteristics of the population.

No. of patients **Total: 100 TB + RB: 70 RB: 30**	Mean	Median	IQR
Age (year)		66	61–71.5
PSA (ng/dL)		6.38	5–9.5
Prostate volume		38.5	29.5–50
DRE			
Normal	86		
Abnormal	14		
No. of lesions per patient (MRI)	3.51	3	1–6
Biopsies per patients (TOT)		11	4–18
Random biopsies		11	0–12
Target biopsies	4.39	4	3–5.25
Core length (mm)			
Target		3.25	2.4–4.43
Random		1.95	1.57–2.18
No. of prior biopsies:			
Primary biopsy		46	
1		29	
2		18	
>3		7	
PIRADS score:			
2		6	
3		30	
4		51	
5		13	

Histology

Each biopsy core was labeled, processed, and examined separately by our expert uropathologist, who was blinded to MRI results. Clinical significance of PCa was defined according to Epstein et al.[13] criteria: Gleason score > 6 or Gleason score 6 with 50% involvement of PCa per core or PCa detected in more than two cores.

Statistical analysis

To compare variables among different patients' settings, the statistical analysis was based on a *t*-test. The test was designed as a two-tailed test, with 5% Type I error. In particular, a Welch Two Sample *t*-test was used to verify differences in the groups. Univariate regression analysis of the risk factors for Gleason score (age, ER, PSA, prostate volume, RM, PIRADS, number of prior biopsies) was performed and *p* values less than 0.05 were considered statistically significant.

Results

A total of 100 patients were included. We stratified the whole population on the basis of PIRADS score (6 pts with PIRADS 2, 30 pts with PIRADS 3, 51 pts with PIRADS 4 and 13 pts with PIRADS 5), number of previous biopsies (46 pts at primary biopsy, 29 pts with one previous negative biopsy, 18 pts with 2 previous negative biopsies and 7 pts with >3 previous negative biopsies), and the Fusion biopsy modality (random + target (70 pts) and only target (30 pts)).

Overall CDR

The overall CDR was 53% (53/100). In relation to PIRADS score, the overall CDR was 0, 40% (12/30), 56.83% (29/51), and 84% (11/13) for PIRADS 2, 3, 4, and 5, respectively. In relation to number of previous biopsies, the overall CDR was 54.34 % (25/46) for primary biopsy and 34.48% (10/29), 72.22% (13/18) and 71.43% (5/7) for 1, 2, >3 prior negative biopsies, respectively.

The distribution of Gleason score at biopsy in relation to PIRADS and to the number of previous biopsies is specified in Table 2.

CDR in RB + TB and in TB groups

According to biopsy modality, CDR for RB + TB was 50% (35/70) and CDR for TB was 60% (18/30) with a *p* value of 0.3632. Tumor was located outside the suspicious mpMRI focus area (that means RB+ and TB−) in 5/70 cases (4 cases GS 6 and 1 case GS 7), but the total cancer length was less or equal to 0.2 cm. In RB + TB group, 5/70 (7.14%) patients resulted TB+ and also RB+, and 25/70 (35.71%) patients resulted TB+ but RB−.

For RB + TB according to number of previous biopsies, the CDR was 46.87% (15/32), 38% (8/21), 69.23% (9/13), and 75% (3/4) for primary biopsy, 1, 2, >3 prior negative biopsies, respectively, and for only TB, the CDR was 71.42% (10/14), 25% (2/8), 80% (4/5), and 66.66% (2/3) for primary biopsy, 1, 2, >3 prior negative biopsies, respectively, with a *p* value > 0.1.

Table 2 summarizes biopsy results in relation to PIRADS score and to number of previous biopsies, in the whole population and in the RB + TB versus TB groups.

Detection of clinically significant PCa

Regarding the detection of csPCa, see Figures 1 and 2.

Univariate analysis

Finally, we calculated a univariate analysis: in the univariate analysis, PIRADS score is the best predictor of the Gleason score and was significantly associated with this variable (Pearson's coefficient $p < 0.05$) showing a strong positive correlation (beta for PIRADS = 4 is 0.52 and beta for PIRADS = 5 is 1).

Discussion

PCa is the most common tumor in men and actually the third tumor-related cause of death.[1] Over the past 10 years, the widespread use of PSA as a screening test has led to an

Table 2. Cancer detection rate (CDR) and Gleason Pattern in correlation to the number of prior biopsies and PIRADS score.

Biopsy results	No. of patients 100 RB + TB 70 TB 30	CDR	GS 6	GS 7(3 + 4 (4 + 3)	GS 8-10
Overall CDR	53/100	53%	27(50.94%)	21 (39.62%)	5 (9.43%)
CDR **RB + TB**	35/70	50%	17(29.31%)	15 (25.86%)	3 (5.17%)
CDR **TB**	18/30	60% ($p = 0.3632$)	10 (55.55%)	6 (33.33%)	2 (11.11%)
TB neg/RB pos	5	5%	4(80%)	1(20%)	-
CDR in relation to no. of prior biopsies					
Primary Biopsy	46	25/46 (54.34%)	13/25 (52%)	10/25 (40%)	2/25 (8%)
1	29	10/29 (34.48%)	4/10 (40%)	5/10 (50%)	1/10 (10%)
2	18	13/18 (72.22%)	8/13 (61.54%)	4/13 (30.77%)	1/13 (7.69%)
>3	7	5/7 (71.43%)	2/7 (40%)	2/7 (40%)	1/7 (20%)
Primary biopsy RB + TB	32	15/32 (46.87%)			
1	21	8/21 (38.09%)			
2	13	9/13 (69.23%)			
>3	4	3 /4 (75%)			
Primary Biopsy TB	14	10/14 (71.42%)			
1	8	2/8 (25%)			
2	5	4/5 (80%)			
>3	3	2/3 (66.66%) *$p > 0.1$			
CDR in relation to PIRADS score					
PIRADS 2	6	0	-	-	-
PIRADS 3	30	12/30 (40%)	11/12 (91.67%)	1/12 (8.33%)	0
PIRADS 4	51	29/51 (56.86%)	14/29 (48.28%)	13/29 (44.83%)	2/29 (6.9%)
PIRADS 5	13	11/13 (84.62%)	2/11 (18.18%)	6 (54.55%)	3/11 (27.27%)
RB + TB					
2	6				
3	26	10/26 (38%)			
4	31	19/31(61%)			
5	7	6/7 (85%)			
TB					
2					
3	4	2/4 (50%)			
4	20	11/20 (55%)			
5	6	5/6 (83%) *$p > 0.1$			

increased number of clinically insignificant diagnoses of cancer, leading to a concrete possibility of overtreatment.[14] For these reasons, International Guidelines do not recommend PSA as a screening test for early diagnosis of PCa, despite a large European study on PCa screening using PSA test showed a reduction in mortality from PCa.[2,5]

In the last few years, research has been focused on developing more accurate imaging techniques with a view to overcome the actual limits of PSA. Many efforts were spent to identify significant lesions, which represent the real target in order to avoid overtreatment.[15,16] In this contest, mpMRI combining diffusion and dynamic studies has shown favorable results for significant PCa.[17] More recently, several studies showed that mpMRI combined with MRI–US fusion biopsy is a promising method for the diagnosis of PCa, particularly for high-risk PCa.[6,7] Despite these promising results, EAU guidelines recommend mpMRI only in patients with previous negative random biopsy (RB) with suspicious PCa, with a Grade B recommendation.[2]

Real-life studies have gained a growing diffusion because this type of work has the potential to improve the quality and delivery of medical care, to reduce the overall costs and to improve the outcomes by accelerating the understanding of how good is to incorporate new therapies and technologies into everyday clinical practice.[18] To our knowledge, this is the first study that specifically analyzes the role of MRI–US fusion biopsy in everyday clinical practice. In this experience, we report an overall CDR of 53% of which Gleason 6 was 50.9% and Gleason $\geqslant 7$ was 49.1%. Comparing the two groups (RB + TB vs. TB), we observed an overall CDR of 50% and 60%, respectively. Gleason $\geqslant 7$ was interesting because it was 31% in the group of RB + TB and 44% in the group of only TB

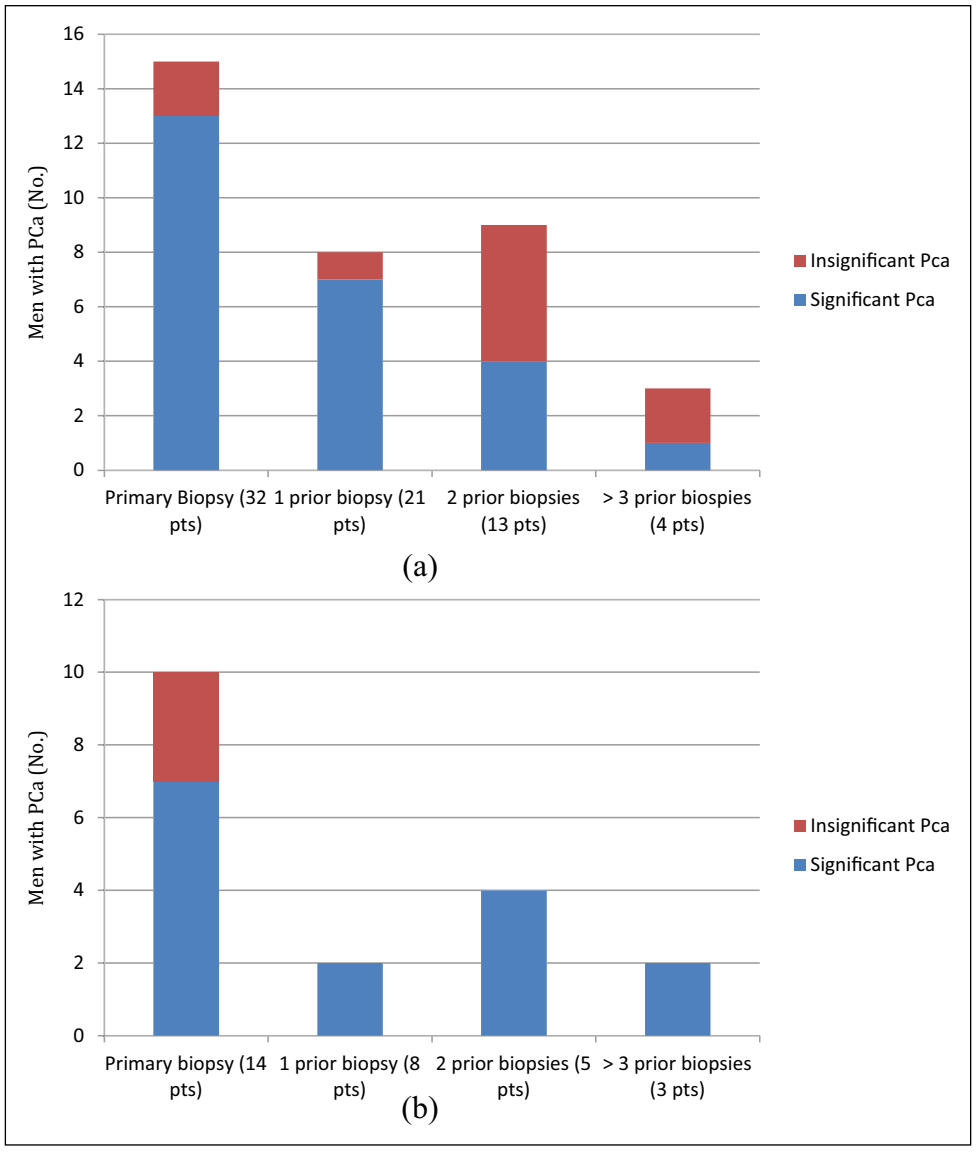

Figure 1. (a) Number of patients with insignificant and significant PCa by the combination of TB/RB in relation to number of prior biopsies. (b) Number of patients with insignificant and significant PCa by combination of TB only (lesion-based biopsy) in relation to number of prior biopsies.

($p = 0.3632$), with considerably fewer cores taken in the group of only TB (6.1 range 3–11 vs. 13.62 range 11–18; $p < 0.05$). Moreover, according to Epstein criteria, in our experience we report a high proportion of csPCa either in the group of RB + TB 25/35 (71%) or in the group of only TB 15/18 (83%). We believe that these results indicate that adding more cores than 12, like in an extended or saturation biopsy protocol, seems to have no meaningful advantages in terms of overall CDR and particularly for clinically significant CDR.[19,20] Mozer et al.[21] in a prospective not randomized experience including only patients at first biopsy observed a high rate of clinically significant cancer in the group of only TB compared with standard RB (12-cores, $p < 0.03$). Sonn et al.[22] reported similar results in a population with previous negative biopsy (21.7% vs. 14.7). In our experience, in a population of first and previous negative biopsy, we did not observe any significant differences between the two groups (TB vs. RB + TB) in terms of clinically significant CDR (83% vs. 71%). On the contrary, in the group of RB + TB, we report a high proportion of insignificant PCa in patients with 2 or 3 previous negative biopsies, with four cases of Gleason 6 and only one case of Gleason 7 located outside the suspicious mpMRI focus area. Moreover, in the group of only TB, we report 3/10 cases of insignificant PCa only in the primary biopsy population and no case in patients with previous negative biopsy (Figure 2). It is true that the group of only TB could be considered a very selected population (two or more lesions classified as PIRADS 4/5); however, the mean PIRADS in the group of RB + TB and TB was 3,52

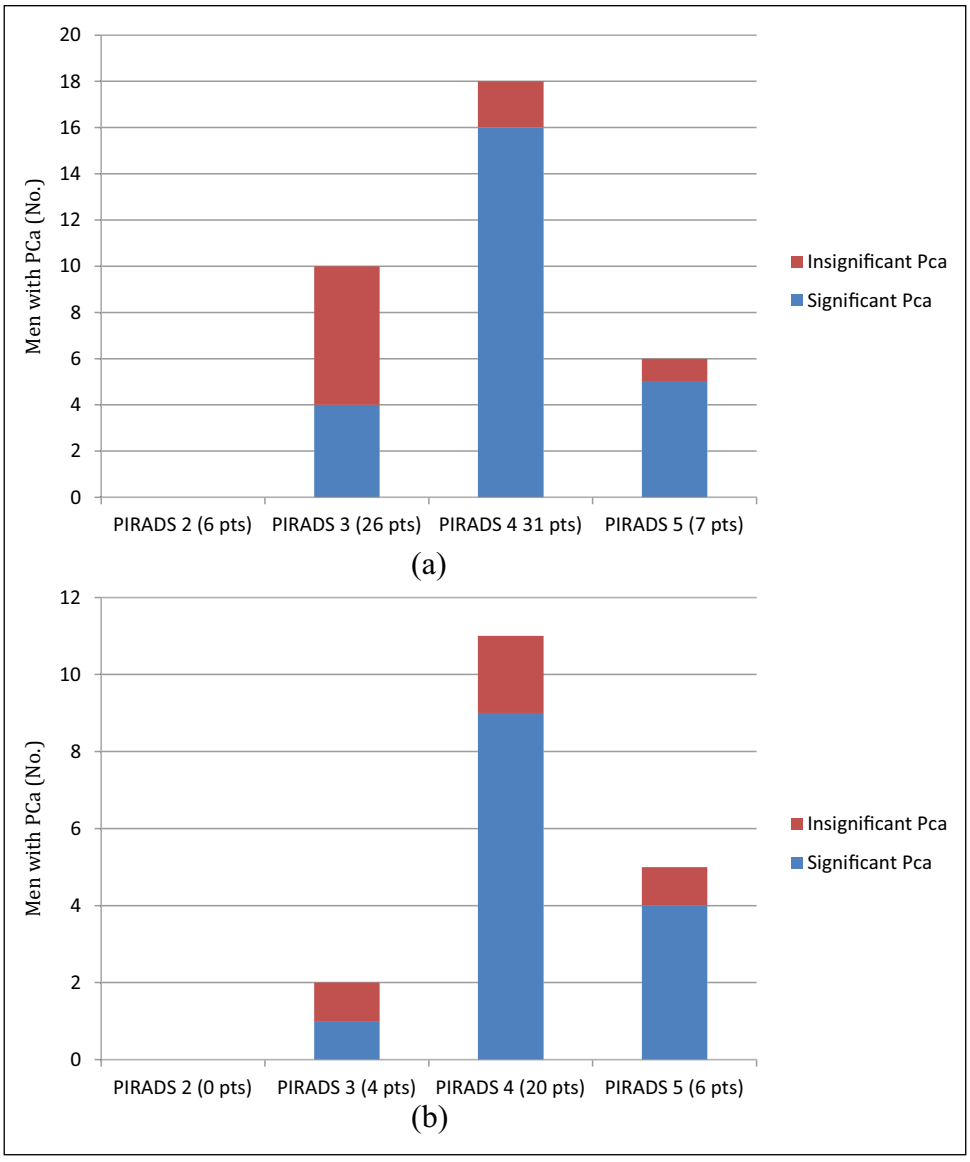

Figure 2. (a) Number of patients with insignificant and significant PCa by the combination of TB/RB in relation to PIRADS score. (b) Number of patients with insignificant and significant PCa by combination of TB only (lesion-based biopsy) in relation to PIRADS score.

and 4.12, respectively. Our data in a homogeneous population such as that in clinical practice seem to confirm the results reported in randomized clinical trials.[6,21,22]

Another important point about the use of MRI–US fusion biopsy in clinical practice is whether the target technique should be followed by random biopsies. Considering our results, we believe that the utility of a standard biopsy in addition to a target one can be considered limited in the naïve population. On the other hand, it should be considered "contraindicated" in patients with previous negative biopsies and suspicious lesions on mpMRI (PIRADS 4/5), given the high percentage of insignificant PCa observed in previous biopsy population comparing the two groups (RB + TB vs. only TB). Arsov et al.[23] reported similar results in a large randomized clinical trial comparing RB + TB with only TB; they concluded that an important improvement in CDR for the combined biopsy approach over MRI-targeted biopsy alone could be excluded in patients with previous negative biopsy. Moreover, same results were reported by Siddiqui et al.[7] that in a large series of 1003 patients at first and repeat biopsy, they concluded that the utility of standard biopsy in addition to targeted biopsy was found to be limited both in a biopsy naive population and in the population with previous negative biopsies. In fact in this study, 200 men were needed to biopsy by standard biopsy in addition to targeted biopsy to diagnose one additional high-risk tumor. Furthermore, for each additional high-risk tumor diagnosed, 17 additional

low-risk tumors would also be diagnosed. Conversely, Borkowetz et al.,[9] in a population with first and repeated biopsies, concluded that more clinically significant cancer (12%) was found by systematic biopsy in addition to target biopsy. Comparing our results of RB + TB group with those reported by Borkowetz et al.'s study showed a significant difference in terms of mean cores taken per patient (21 vs 13.62) and a different approach in RB procedure (transrectal vs transperineal). Moreover, in the study by Borkowetz et al., adding a systematic random biopsy to a target biopsy detects 50% more tumors with clinically insignificant Gleason score 6. We believe that a transrectal approach and a mean number 21 cores, which is comparable with a saturation biopsy model, do not represent the standard for clinical practice. Our results are similar to those reported by Siddiqui et al.[7] where the number of cores taken per patient was comparable with our experience either for target model or for systematic random model, but in the group of SB + TB we report only one in Gleason 7 located outside the mpMRI focus area.

Our results support those reported by Siddiqui et al.[7] We suggest that in patients with previous RB and two or more lesions classified as PIRADS 3/4/5 on MRI, only TB is a reasonable approach to ensure a high CDR of csPCa and to reduce the diagnosis of insignificant ones. Moreover, we believe that in patients with previous negative RB a prospective comparison between MRI-targeted biopsy alone and systematic TRUS-biopsy is now justified.

Our study has some limitations: it is a single-centered study with a limited population which could raise the question of whether our results are reproducible in other centers. In our experience, the mpMRI was made by radiologists with vast experience (more than 10 years) with mpMRI interpretation and it is well known how there can be a different interpretation of PIRADS score among different centers as reported recently by Hansen et al. They observed a disagreement between initial and tertiary centers in 54% of cases.[24] We believe that this is a crucial point for the reproducibility of the method in clinical practice; however, the increasing popularity of mpMRI in primary centers and the consensus meeting between radiologists could lead in the near future to greater uniformity of image interpretation. Another limitation of our study was that patients with negative mpMRI were excluded from the trial. However, the high negative predictive value of mpMRI (86%), especially for Gleason 7 or greater (98%), supports our design.[17] Moreover, we had performed only TB in a very selected population (two or more lesions PIRADS 3/4/5). On the other hand, the rate of significant cancer in relation to PIRADS 4–5 was reported to be very high in several experiences (74%–98%)[6] and range between 80% and 83% in our study population. In our study, univariate analysis shows that PIRADS score is the best predictor for Gleason score and it was significantly associated with this variable.

Conclusions

In conclusion, in our experience, MRI–US fusion biopsy (RB + TB and only TB) is associated with a high CDR of csPCa. Moreover, MRI–US fusion biopsy (only TB) could be a reasonable approach in patients with a previous negative biopsy and high PIRADS score on MRI, to ensure a high CDR of significant PCa and to reduce the diagnosis of insignificant ones. Further randomized clinical trials are necessary to establish the right role of MRI–US fusion biopsy (only TB) in clinical practice.

Acknowledgements

They also declare that they have full control of all primary data and that they agree to allow the journal to review their data if requested.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66(1): 7–30.
2. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1.
3. Zackrisson B, Aus G, Bergdahl S, et al. The risk of finding focal cancer (less than 3 mm) remains high on re-biopsy of patients with persistently increased prostate specific antigen but the clinical significance is questionable. *J Urol* 2004; 171(4): 1500–1503.
4. de Rooij M, Hamoen EH, Witjes JA, et al. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. *Eur Urol* 2016; 70: 233–245.
5. American Urological Association. White Paper: AUA/Optimal Techniques of Prostate Biopsy and Specimen Handling.
6. 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(1): 8–19.
7. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015; 313(4): 390–397.
8. Cash H, Maxeiner A, Stephan C, 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* 2015; 34: 525–532.
9. Borkowetz A, Platzek I, Toma M, et al. Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer. *BJU Int* 2015; 116(6): 873–879.
10. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly

upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol* 2013; 64(5): 713–719.
11. Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013; 189(3): 860–866.
12. van den Bergh RC and van der Poel HG. Re: Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64:713–9 and Re: Emberton M. Has magnetic resonance-guided biopsy of the prostate become the standard of care? Eur Urol 2013; 64:720–1. *Eur Urol* 2014; 65(6): e106–e107.
13. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol* 2016; 40(2): 244–252.
14. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012; 366(11): 981–990.
15. Sciarra A, Barentsz J, Bjartell A, et al. Advances in magnetic resonance imaging: how they are changing the management of prostate cancer. *Eur Urol* 2011; 59(6): 962–977.
16. Rowe SP, Gorin MA, Allaf ME, et al. PET imaging of prostate-specific membrane antigen in prostate cancer: current state of the art and future challenges. *Prostate Cancer Prostatic Dis* 2016; 19(3): 223–230.
17. Sciarra A, Panebianco V, Ciccariello M, et al. Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. *Clin Cancer Res* 2010; 16(6): 1875–1883.
18. Rizzo M, Carteni G and Pappagallo G. We need both randomized trials and real-world data: the example of everolimus as second-line therapy for mRCC. *Future Oncol* 2014; 10(12): 1893–1896.
19. Ting F, Van Leeuwen PJ, Thompson J, et al. Assessment of the performance of magnetic resonance imaging/ultrasound fusion guided prostate biopsy against a combined targeted plus systematic biopsy approach using 24-core transperineal template saturation mapping prostate biopsy. *Prostate Cancer* 2016; 2016: 3794738.
20. Radtke JP, Kuru TH, Bonekamp D, et al. Further reduction of disqualification rates by additional MRI-targeted biopsy with transperineal saturation biopsy compared with standard 12-core systematic biopsies for the selection of prostate cancer patients for active surveillance. *Prostate Cancer Prostatic Dis* 2016; 19(3): 283–291.
21. Mozer P, Rouprêt M, LeCossec C, et al. First round of targeted biopsies using magnetic resonance imaging/ultrasonography fusion compared with conventional transrectal ultrasonography-guided biopsies for the diagnosis of localised prostate cancer. *BJU Int* 2015; 115(1): 50–57.
22. 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(4): 809–815.
23. 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(4): 713–720.
24. Hansen NL, Koo BC, Gallagher FA, et al. Comparison of initial and tertiary centre second opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy. *Eur Radiol* 2016; 27: 2259–2266.