INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2018) doi: 10.1111/iju.13796

Original Article

Accuracy of elastic fusion biopsy in daily practice: Results of a multicenter study of 2115 patients

Marco Oderda,[1,2] Giancarlo Marra,[1] Simone Albisinni,[3] Emanuela Altobelli,[4] Eduard Baco,[5] Valerio Beatrici,[6] Andrea Cantiani,[7] Antonio Carbone,[8] Mauro Ciccariello,[9] Jean-Luc Descotes,[10] Marine Dubreuil-Chambardel,[11] David Eldred-Evans,[12] Giuseppe Fasolis,[2] Mariaconsiglia Ferriero,[13] Gaelle Fiard,[10] Valerio Forte,[9] Alessandro Giacobbe,[14] Pardeep Kumar,[12] Vito Lacetera,[6] Pierre Mozer,[15] Giovanni Muto,[14] Rocco Papalia,[4] Antonio Pastore,[8] Alexandre Peltier,[16] Thierry Piechaud,[17] Giuseppe Simone,[13] Jean-Baptiste Roche,[17] Morgan Roupret,[15] Olivier Rouviere,[11] Roland Van Velthoven[16] and Paolo Gontero[1]

[1]Department of Surgical Sciences - Urology, University of Turin, Turin, [2]Department of Urology, San Lazzaro Hospital, Alba, Italy, [3]Department of Urology, Hopital Erasme, Université Libre de Bruxelles, Brussels, Belgium, [4]Department of Urology, Campus Biomedico University, Rome, Italy, [5]Department of Urology, Oslo University Hospital, Oslo, Norway, [6]Department of Urology, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro-Fano, [7]Department of Urology, San Maria Hospital, Terni, [8]Department of Medico-Surgical Sciences and Biotechnologies, Urology Unit, Sapienza University of Rome, Latina, [9]Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University of Rome, Rome, Italy, [10]Department of Urology, Centre Hospitalier Universitaire de Grenoble, Grenoble, [11]Hospices Civils de Lyon, Department of Urinary and Vascular Radiology, Hôpital Edouard Herriot, Université de Lyon, Lyon, France, [12]Department of Urology, Royal Marsden Hospital, London, UK, [13]Department of Urology, Regina Elena National Cancer Institute, Rome, [14]Department of Urology, Humanitas Gradenigo Hospital, Turin, Italy, [15]Department of Urology, Pitié Salpétrière Hospital, Assistance Publique - Hôpitaux de Paris, Universités Paris Sorbonne, Paris, France, [16]Department of Urology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, and [17]Department of Urology, Clinique Saint Augustin, Bordeaux, France

Abbreviations & Acronyms
CDR = cancer detection rate
DRE = digital rectal examination
mpMRI = multiparametric magnetic resonance imaging
PCa = prostate cancer
PET = positron-emission tomography
PI-RADS = Prostate Imaging Reporting and Data System
PRIAS = Prostate Cancer Research International Active Surveillance
PSA = prostate-specific antigen
STARD = Standards for Reporting Diagnostic accuracy studies
TRUS = transrectal ultrasound

Correspondence: Marco Oderda M.D., F.E.B.U., Department of Surgical Sciences - Urology, University of Turin, Via Giuseppe Verdi 8, Turin 10124, Italy.
Email: marco.oderda@libero.it

Received 29 May 2018; accepted 5 August 2018.

Objectives: To assess the accuracy of Koelis fusion biopsy for the detection of prostate cancer and clinically significant prostate cancer in the everyday practice.
Methods: We retrospectively enrolled 2115 patients from 15 institutions in four European countries undergoing transrectal Koelis fusion biopsy from 2010 to 2017. A variable number of target (usually 2–4) and random cores (usually 10–14) were carried out, depending on the clinical case and institution habits. The overall and clinically significant prostate cancer detection rates were assessed, evaluating the diagnostic role of additional random biopsies. The cancer detection rate was correlated to multiparametric magnetic resonance imaging features and clinical variables.
Results: The mean number of targeted and random cores taken were 3.9 (standard deviation 2.1) and 10.5 (standard deviation 5.0), respectively. The cancer detection rate of Koelis biopsies was 58% for all cancers and 43% for clinically significant prostate cancer. The performance of additional, random cores improved the cancer detection rate of 13% for all cancers ($P < 0.001$) and 9% for clinically significant prostate cancer ($P < 0.001$). Prostate cancer was detected in 31%, 66% and 89% of patients with lesions scored as Prostate Imaging Reporting and Data System 3, 4 and 5, respectively. Clinical stage and Prostate Imaging Reporting and Data System score were predictors of prostate cancer detection in multivariate analyses. Prostate-specific antigen was associated with prostate cancer detection only for clinically significant prostate cancer.
Conclusions: Koelis fusion biopsy offers a good cancer detection rate, which is increased in patients with a high Prostate Imaging Reporting and Data System score and clinical stage. The performance of additional, random cores seems unavoidable for correct sampling. In our experience, the Prostate Imaging Reporting and Data System score and clinical stage are predictors of prostate cancer and clinically significant prostate cancer detection; prostate-specific antigen is associated only with clinically significant prostate cancer detection, and a higher number of biopsy cores are not associated with a higher cancer detection rate.

Key words: accuracy, fusion biopsy, Koelis, random, targeted.

Introduction

In recent years, mpMRI has become a key element in the diagnosis and management of PCa.[1] The advent of mpMRI-targeted biopsies has improved the CDR, usually estimated to be approximately 33%, and in particular the detection of clinically significant cancers.[2–6] In-bore mpMRI biopsies are the most precise, but are also costly, time-consuming and less reproducible. In contrast, TRUS-mpMRI fusion biopsies achieve good results with acceptable costs, good reproducibility and accessibility for the patient. Fusion biopsies have been shown to be superior to cognitive biopsies, and they are now routinely carried out when a lesion is detected at mpMRI.[7] However, to date, several challenges exist regarding the implementation of TRUS-mpMRI fusion biopsies in clinical practice: among these, the inaccurate reading of mpMRI, which should be restricted to dedicated radiologists;[5] the presence of approximately 10% of significant cancers invisible to mpMRI;[8] the inaccurate sampling of lesions during fusion biopsy, as a result of inaccurate segmentation of mpMRI images or registration;[9] and last, but not least, mechanical error of the device used. Keeping in mind these limitations, TRUS-mpMRI fusion biopsies are highly utilized for targeted biopsy of the prostate, using different devices.[5] Among these, Koelis has shown a good targeting precision of <3 mm on prostate phantoms,[6] and an acceptable margin of error also in clinical practice.[10] Once the initial learning curve is completed, biopsies are easily carried out, usually under local anesthesia. Since the original Koelis Urostation, technological progress has been made with the new-generation Koelis Trinity. The aim of the present multicenter, retrospective study was to assess the accuracy of Koelis fusion biopsy for the detection of PCa in everyday practice on a large number of patients, providing data on the reliability of the device across different European institutions.

Methods

This was a retrospective, multicenter study including 2115 consecutive patients from 15 institutions in four European countries (Italy, France, Belgium, the UK), who underwent transrectal TRUS-mpMRI fusion biopsy with the Koelis system between 2010 and 2017. All data were anonymized and inserted in a global database. All patients had at least one suspicious lesion at mpMRI. The primary end-points of study were the overall and clinically significant CDR of Koelis fusion biopsies. The secondary end-points included the diagnostic role of additional random biopsies, and the correlation between PCa and clinical or mpMRI parameters, and complications of the procedure reported according to the Clavien–Dindo classification.[11] All patients signed informed consent for the use of clinical information for clinical studies. The study was carried out according to the STARD.[12]

mpMRI and biopsy details

mpMRI were carried out in different centers, sometimes independent from the institution where the biopsy was carried out, as often happens in daily practice. Therefore, no data about the mpMPI protocol used were available. The suspicious lesions were scored according to the PI-RADS classification, version 1[13] up to 2015, and successively version 2.[14]

Fusion biopsies were carried out with the Koelis system (Koelis, Meylan, France) using the Koelis Urostation in 88.7% of patients, and the more recent Koelis Trinity in the remaining 11.3%. A variable number of targeted biopsies (usually 2–4) and random biopsies (usually 10–14) were carried out, depending on the clinical case, urologist preference and institution habits. Koelis Trinity system creates a precise and highly detailed 3-D map of the prostate, showing the biopsy cores locations and suspicious areas delineated on MRI or PET sequences. Trinity integrates 3-D ultrasound, multimodal elastic fusion and Organ-Based Tracking, which is the only tracking technology available working with image-based tracking. During the examination, a 3-D TRUS probe creates a 3-D reference model of the prostate; new images are taken to register the location of the biopsy needle at each biopsy. Thanks to the organ-based technology, the device follows the position of the prostate and not that of the probe, automatically compensating for patient movement and prostate deformation. Koelis Urostation is an older mobile software platform that required a connection and communication with an external ultrasound system, whereas Koelis Trinity is a fully-integrated platform, more recently released on the market.

All biopsies in the present study were carried out with a transrectal approach by experienced urologists dedicated to fusion biopsy with Koelis (namely, >50 biopsies carried out with Koelis).

PCa was considered clinically significant in the case of findings of a Gleason score ≥7 or three or more cores of Gleason score 6, as suggested by histological criteria of PRIAS.[15]

Statistical analysis

Statistical analyses were carried out with SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). The Mann–Whitney *U*-test was used to compare the distribution of continuous variables, whereas the Fisher's exact and Pearson's χ^2-tests were used to compare proportions of categorical variables. To identify predictors of PCa detection, univariate logistic regression was carried out initially to obtain unadjusted hazard ratios. Subsequently, all statistically significant variables were put into a multivariate model to obtain adjusted hazard ratios. Variables of interest for logistic regression were PSA, clinical stage, target size, number of targets, PI-RADS score and the number of cores taken. A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline patients' characteristics

The mean patients' characteristics are shown in Table 1 together with mpMRI and biopsy features. Most patients enrolled had negative DRE (76%) and PSA ≤10 ng/mL (74%). Almost half of the patients were biopsy-naïve,

Table 1 Baseline patients' characteristics, mpMRI features and biopsy details

Patients' characteristics	
Median age, years (range)	66 (41–86)
Mean PSA, ng/mL (SD)	8.4 (7.4)
PSA density (ng/mL)	0.18 (0.19)
DRE	
Negative	1195 (76.1%)
Positive	377 (23.9%)
missing	543
Mean prostate volume, cc (SD)	52.7 (27.1)
Median prostate volume, cc (range)	47 (13–226)
Previous biopsies	
Biopsy-naïve	705 (46.7%)
Previous negative biopsies	741 (49.1%)
Patients in active surveillance	63 (4.2%)
Missing	606
mpMRI features	
mpMRI targets for patient	
Single	1754 (82.9%)
Multiple	361 (17.1%)
Mean size of targets, mm (SD)	10.6 (7.3)
PI-RADS of targets (maximum score in case of multiple targets)	
3	677 (34.2%)
4	902 (45.3%)
5	409 (20.5%)
Missing	127
Biopsy details	
Device	
Koelis Urostation	1875 (88.7%)
Koelis Trinity	240 (11.3%)
Targeted cores taken	
Mean (SD)	3.9 (2.1)
Median (range)	4.0 (1–18)
Random cores taken	
Mean (SD)	10.5 (5.0)
Median (range)	12 (0–32)
Random cores taken in addition to targeted cores	
0	111 (5.4%)
1–11	654 (31.7%)
12–14	1092 (52.9%)
≥15	208 (10.0%)
Missing	50
Total cores taken	
Mean (SD)	14.4 (5.3)
Median (range)	14 (2–50)

whereas 4% followed a protocol of active surveillance. mpMRI targets were single in the majority of cases (83%). The mean number of targeted and random cores taken were 3.9 (SD 2.1) and 10.5 (SD 5.0), respectively. A variable number of additional random cores were taken for each patient; most commonly, a scheme of 12–14 cores was used (53% of cases), whereas 5% of patients received targeted biopsies only. The procedure was well tolerated, with only minor complications reported (all grade II; urinary infection rate <5%).

Biopsy outcomes

Biopsy outcomes are reported in Table 2. The CDR of Koelis biopsies was 58% for all cancers and 43% for clinically significant PCa. When considering targeted biopsies only, the CDR was 46% for all cancers and 34% for clinically significant PCa.

Table 2 Biopsy results in terms of PCa and clinically significant PCa detection, comparing target biopsies only with target + random biopsies

	Target biopsies only	Target + random biopsies	*P*
PCa detection on biopsy			
CDR	965 (45.6%)	1230 (58.2%)	<0.001
PCa Gleason score			
GS 6	357 (37.3%)	461 (40.1%)	0.14
GS 7	437 (45.7%)	493 (42.8%)	0.25
GS 8–10	162 (16.9%)	197 (17.1%)	0.86
Missing	9	79	
PCa detection according to DRE			
Negative	494 (65.9%)	664 (69.0%)	0.17
Positive	256 (34.1%)	299 (31.0%)	0.17
Missing	215	266	
PCa detection according to size			
<10 mm	256 (45.6%)	305 (46.7%)	0.70
≥10 mm	305 (54.4%)	348 (53.3%)	0.70
Missing	404	577	
PCa detection according to PI-RADS			
3	144 (15.7%)	208 (17.8%)	0.20
4	450 (49.0%)	595 (51.0%)	0.36
5	325 (35.4%)	363 (31.1%)	0.03
Missing	46	64	
PCa detection according to previous biopsy			
Biopsy naïve	371 (52.9%)	420 (48.6%)	0.08
Previous negative biopsies	299 (42.7%)	393 (45.4%)	0.27
Patients in active surveillance	31 (4.4%)	52 (6%)	0.16
Missing	264	365	
Clinically significant PCa detection on biopsy			
Clinically significant CDR	716 (33.9%)	909 (43.0%)	<0.001
Clinically significant PCa detection according to PI-RADS			
3	77 (11.3%)	114 (13.2%)	0.29
4	334 (48.9%)	426 (49.4%)	0.84
5	272 (39.8%)	323 (37.4%)	0.36
Missing	33	48	

The performance of additional, random cores improved the CDR of 13% for all cancers and 9% for clinically significant PCa; in both cases, the differences were statistically significant ($P < 0.001$). Additional, random cores allowed the detection of an upgrade from Gleason 6 to 7 in 11% of patients, and from Gleason 7 to 8 in 6% of patients. Only one patient was upgraded from Gleason 6 to 8. PCa was detected in 31%, 66% and 89% of patients with lesions scored as PI-RADS 3, 4 and 5, respectively. Clinically significant PCa was detected in 17%, 47% and 79% of lesions scored as PI-RADS 3, 4 and 5, respectively (Fig. 1). An increase in Gleason score was noted with the increase of PI-RADS score (Fig. 2). The improvement of CDR as a result of additional, random cores was shown independently from the version of PI-RADS used (Table S1); PCa was more likely to be found in lesions scored as PI-RADS 5 in version 1.0 (93.3%), rather than version 2.0 (81.0%; Fig. S1).

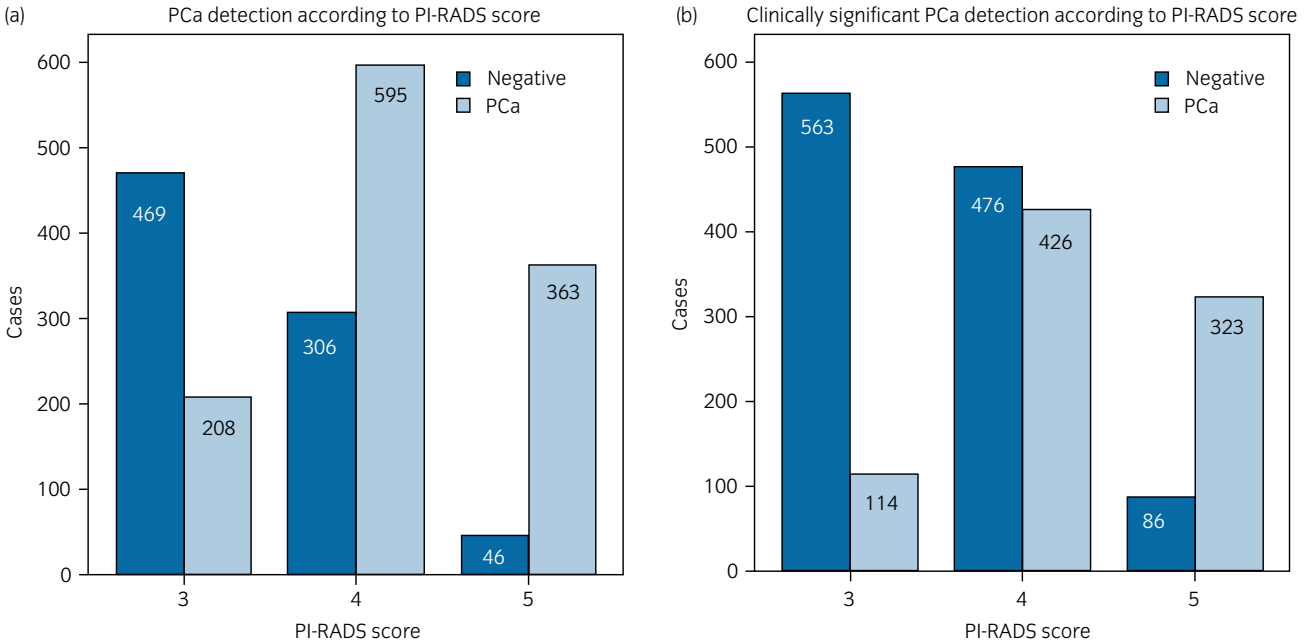

Fig. 1 (a) PCa detection according to PI-RADS score; (b) clinically significant PCa detection according to PI-RADS score.

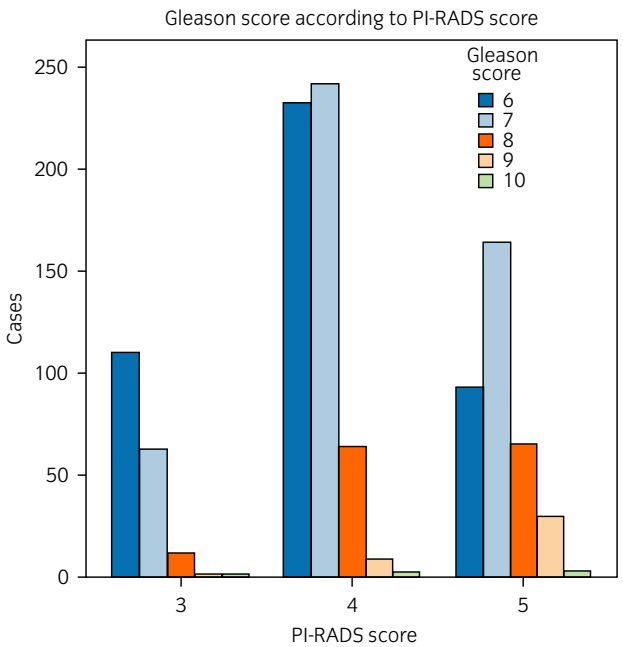

Fig. 2 Gleason score findings according to PI-RADS score.

Predictors of PCa at biopsy

Considering target biopsies only, PSA, positive DRE, target size ≥10 mm, multiple targets, elevated PI-RADS score and biopsy-naïve status correlated with PCa detection. Multivariate analyses confirmed this association only for positive DRE and elevated PI-RADS score (Table 3). As for clinically significant PCa, multivariate analyses found positive DRE, PI-RADS score and also PSA to be predictors of PCa detection (Table 4).

Considering target plus random biopsies, positive DRE and elevated PI-RADS score were the only predictors of PCa in multivariate analyses. The number of cores taken was associated with PCa, but only in univariate analyses (Table 3). As for clinically significant PCa, PSA, positive DRE and PI-RADS score were again associated with PCa detection (Table 4).

Discussion

The technique of prostate biopsy has been revolutionized in recent years with the advent of mpMRI/TRUS fusion biopsies. Among the devices used for this goal, Koelis is supported by quite robust evidence, showing a CDR ranging from 48% to 80%.[6,7,16–22] When deciding to use a device for fusion biopsy, its precision, safety and ease of use are essential parameters to be considered. However, several other factors must also be taken into account, such as the reliability of mpMRI, the skill of the operator and the presence of cancers still invisible to mpMRI.[8]

Most of the studies published to date on fusion biopsy are single-center, small-sized and based on mpMRIs carried out in high-volume centers by dedicated radiologists, thus limiting their reproducibility. To overcome these limitations, our multicenter study has gathered data from different European institutions, with the aim to provide data on the accuracy of Koelis coming from daily practice. All urologists included in the study were experienced in Koelis fusion biopsy with >50 procedures carried out each, as the influence of experience in the accuracy of the fusion biopsy has been well demonstrated.[10]

It is difficult to assess the real CDR of fusion biopsy, considering the heterogeneity of devices used. A recent review found that mpMRI-TRUS image fusion biopsy achieves a

Table 3 Predictors of PCa detection on target biopsies only and in target + random biopsies

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
PCa detected on target biopsies only				
PSA	1.02 (1.00–1.03)	0.003	1.02 (0.99–1.05)	0.57
DRE				
Negative	Ref	–	Ref	–
Positive	3.00 (2.35–3.83)	<0.001	2.49 (1.73–3.57)	<0.001
Target size				
<10 mm	Ref	–	Ref	–
≥10 mm	1.52 (1.19–1.94)	0.001	1.08 (0.81–1.45)	0.56
No. targets				
Single	Ref	–	Ref	–
Multiple	1.42 (1.13–1.78)	0.002	1.38 (0.95–1.99)	0.08
Maximum PI-RADS score				
3	Ref	–	Ref	–
4	3.68 (2.94–4.61)	<0.001	2.22 (1.61–3.06)	<0.001
5	14.32 (10.58–19.37)	<0.001	6.93 (4.64–10.35)	<0.001
No. target cores taken	1.02 (0.98–1.06)	0.30	–	–
Previous biopsies				
No	Ref	–	Ref	
Yes	0.62 (0.51–0.76)	<0.001	0.75 (0.54–1.06)	0.10
PCa detected on target + random biopsies				
PSA	1.02 (1.01–1.04)	0.001	1.02 (0.99–1.05)	0.16
DRE				
Negative	Ref		Ref	–
Positive	3.08 (2.34–4.06)	<0.001	2.43 (1.65–3.58)	<0.001
Target size				
<10 mm	Ref	–	Ref	–
≥10 mm	1.50 (1.17–1.93)	0.001	0.99 (0.73–1.33)	0.99
No. targets				
Single	Ref	–	Ref	–
Multiple	1.45 (1.14–1.83)	0.002	1.18 (0.81–1.72)	0.37
Maximum PI-RADS score				
3	Ref	–	Ref	–
4	4.37 (3.53–5.42)	<0.001	2.21 (1.61–3.02)	<0.001
5	17.74 (12.53–25.11)	<0.001	8.30 (5.35–12.86)	<0.001
No. target + random cores taken	1.03 (1.01–1.05)	<0.001	1.04 (0.99–1.10)	0.07
Previous biopsies				
No	Ref	–	–	–
Yes	0.08 (0.68–1.03)	0.09	–	–

median detection rate of any PCa of 50.5%, including five different softwares.[4] According to the present results, the overall CDR of Koelis biopsies is 58%, which is in line with other studies focused on the Koelis system.[7,16,17,20] The CDR decreases to 42% when focusing only on clinically significant PCa. However, what PCa is really to be considered as clinically significant? This definition varies greatly between studies, reflecting the uncertainty of identifying the determinants of cancer progression on biopsy.[4] In the present study, we considered the finding of Gleason score 7 or more, or more than two cores of Gleason score 6 as clinically significant, following the histological criteria of the PRIAS study.[15] In the literature, there is no definitive consensus about the definition of clinically significant PCa, but we thought it best to use the criteria that define a cancer to be addressable to active surveillance or not. When dealing with fusion biopsy, it is still not clear how to consider multiple positive cores taken from the same target. Some authors suggest to consider them as a single positivity, as they come from the same lesion, but cancer volume and target size must be taken into account. As there are no clear recommendations in this field, we chose to consider every single positive core for the assessment of clinically significant PCa. Some other studies used cancer core length as a surrogate marker of cancer volume, even if the exact threshold to define the lesion as clinically significant is not clear.[4]

Another debated issue is represented by the utility of random biopsies in addition to target biopsies. Should we rely only on target biopsies only? A prospective study of 1003 patients undergoing both targeted (UroNav, Invivo, Gainesville, FL, USA) and standard biopsy found that targeted biopsy diagnosed 30% more high-risk cancers and 17% fewer low-risk cancers.[23] Nevertheless, it has been reported that up to 17% of significant PCa is missed by target biopsy only, prompting the execution of an additional, standard biopsy.[8] Nowadays, the combination of target and random biopsies

Table 4 Predictors of clinically significant PCa detection on target biopsies only and in target + random biopsies

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Clinically significant PCa detected on target biopsies only				
PSA	1.03 (1.02–1.05)	<0.001	1.05 (1.02–1.08)	0.001
DRE				
Negative	Ref	–	Ref	–
Positive	3.29 (2.59–4.18)	<0.001	3.13 (2.01–4.87)	<0.001
Target size				
<10 mm	Ref	–	Ref	–
≥10 mm	1.67 (1.29–2.15)	<0.001	0.93 (0.64–1.35)	0.71
No. targets				
Single	Ref	–	–	–
Multiple	1.25 (0.99–1.59)	0.05	–	–
Maximum PI-RADS score				
3	Ref	–	Ref	–
4	4.58 (3.48–6.02)	<0.001	2.10 (1.37–3.24)	0.001
5	15.47 (11.30–21.17)	<0.001	5.24 (3.13–8.77)	<0.001
No. target cores taken	1.08 (1.03–1.13)	<0.001	1.05 (1.02–1.08)	0.32
Previous biopsies				
No	Ref	–	Ref	–
Yes	0.68 (0.55–0.85)	0.001	0.89 (0.61–1.29)	0.55
Clinically significant PCa detected on target + random biopsies				
PSA	1.02 (1.01–1.03)	0.002	1.05 (1.02–1.09)	0.001
DRE				
Negative	Ref	–	Ref	–
Positive	3.07 (2.41–3.91)	<0.001	2.58 (1.68–3.97)	<0.001
Target size				
<10 mm	Ref	–	Ref	–
≥10 mm	1.53 (1.20–1.95)	0.001	0.80 (0.56–1.11)	0.24
No. targets				
Single	Ref	–	–	–
Multiple	1.23 (0.98–1.55)	0.06	–	–
Maximum PI-RADS score				
3	Ref	–	Ref	–
4	4.42 (3.47–5.61)	<0.001	2.03 (1.38–2.98)	<0.001
5	18.54 (13.58–25.39)	<0.001	5.47 (3.32–9.01)	<0.001
No. target + random cores taken	1.02 (1.00–1.03)	0.01	1.00 (0.94–1.05)	0.98
Previous biopsies				
No	Ref	–	Ref	–
Yes	0.69 (0.56–0.85)	0.001	0.77 (0.54–1.09)	0.15

represents the standard for PCa detection; the present study strengthens this recommendation, showing that additional, random cores improved the CDR for all PCa of 13%, and that of clinically significant PCa of 9%. We must keep in mind that our patients underwent a variable number of random biopsies, being less than the usual 12–14 cores in >30% of the cohort.

A recent study on 564 patients newly diagnosed with PCa has shown that systematic biopsy over fusion one (UroNav, Invivo) upgraded PCa from Gleason 6 to 7 in 5%, and from Gleason 7 to 8 in 1% of patients. The present results, drawn from a larger series of patients, are quite different, showing an upgrade from Gleason 6 to 7 in 11% of patients, and from Gleason 7 to 8 in 6% of patients. A possible explanation for this diversity might be due to the different populations in the study: the present series of patients was more heterogeneous and possibly exposed to a greater risk of harboring a significant PCa outside of the lesions detected at the mpMRI, given that it includes patients whose mpMRIs were not carried out in the same center of the fusion biopsy, and sometimes interpreted by radiologists not dedicated to prostate imaging. The diagnostic advantage of Koelis fusion biopsy over a standard biopsy, however, is not in doubt, considering the overall per-patient CDR of 58%, a percentage much higher than that reported for standard biopsies, approximately 33–36%.[24]

A linear relationship has been suggested between PI-RADS and Gleason score, reflecting the cellular density of the region of interest.[25] Following this lead, the present results showed a higher probability of finding PCa with an elevated Gleason score in the case of PI-RADS 4 or 5. The uncertainty of this correlation, however, is highlighted by the non-negligible proportion of patients harboring PI-RADS 5 lesions that resulted in being Gleason 6 PCa, or no cancer at all. Sometimes, an intense granulomatous inflammation of the prostate can mimic an aggressive cancer at mpMRI, as was noted in some of our 46 patients who were negative at biopsy

even in the presence of PI-RADS 5 lesions. In contrast, some lesions might have been simply missed by fusion biopsy. To overcome these diagnostic inaccuracies, continuous feedback between urologists, pathologists and radiologists dedicated to fusion biopsy is required to ensure good quality of the procedure. Unfortunately, in everyday clinical practice, it is not easy to maintain good standards, especially if mpMRIs are carried out in centers not dedicated to prostate imaging.

When analyzing the correlation between PI-RADS score and PCa, we have to remember that PI-RADS classification was updated in 2015; however, the adoption of the new classification did not affect the present results, with the addition of random cores still leading to a significant improvement in CDR. Interestingly, with the adoption of PI-RADS version 2.0, more lesions scored as PI-RADS 5 resulted negative for cancer, possibly reflecting the need for a learning curve in MRI interpretation by radiologists.

Regarding the predictors of overall cancer detection at fusion biopsy, only clinical stage and PI-RADS score showed a significant association at multivariate analyses. It is interesting to remark that the number of cores taken was not a predictor of PCa detection, adding another point against the old saturation biopsy. As for the prediction of clinically significant cancers, the old, maltreated PSA seems to reacquire an important diagnostic role, together with the usual clinical stage and PI-RADS score. On the contrary, target size was not a strong predictor of cancer, reflecting again the uncertainties of the mpMRI.

To our knowledge, the present study gathered the largest series of fusion biopsies reported to date, but is not devoid of limitations, mostly inherent to its retrospective design. The main limitations were the lack of a control group, the lack of data regarding mpMRI protocols and types, the lack of a central revision of mpMRI images and bioptic specimens, and the absence of a standardized protocol of random biopsies, which did not allow a proper comparison between targeted and systematic biopsies. In contrast, the heterogeneity of our cohort can be seen as a strength of this study, which shows the outcomes of Koelis fusion biopsy in everyday practice, where mpMRIs are carried out in centers with different degrees of expertise and patients cannot be selected.

In conclusion, under routine conditions, fusion biopsy with Koelis achieves a good CDR, which increases in patients with a high PI-RADS score and clinical stage. The performance of additional, random cores seems unavoidable for correct sampling. PI-RADS and clinical stage are the strongest predictors of PCa detection, whereas PSA showed an association only for clinically significant PCa. The number of cores taken was not associated with higher CDR.

Conflict of interest

Marco Oderda, Pierre Mozer and Roland Van Velthoven have worked as consultants for Koelis.

References

1 Dickinson L, Ahmed HU, Allen C *et al.* Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. *Eur. Urol.* 2011; **59**: 477–94.

2 Fütterer 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.

3 Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink M. 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. *Eur. Urol.* 2015; **68**: 438–50.

4 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.

5 Verma S, Choyke PL, Eberhardt SC *et al.* The current state of MR imaging-targeted biopsy techniques for detection of prostate cancer. *Radiology* 2017; **285**: 343–56.

6 Ukimura O, Desai MM, Palmer S *et al.* 3-Dimensional elastic registration system of prostate biopsy location by real-time 3-dimensional transrectal ultrasound guidance with magnetic resonance/transrectal ultrasound image fusion. *J. Urol.* 2012; **187**: 1080–6.

7 Oderda M, Faletti R, Battisti G *et al.* Prostate cancer detection rate with Koelis™ fusion biopsies versus cognitive biopsies: a comparative study. *Urol. Int.* 2016; **97**: 230–7.

8 Radtke JP, Teber D, Hohenfellner M, Hadaschik BA. The current and future role of magnetic resonance imaging in prostate cancer detection and management. *Transl. Anrol. Urol.* 2015; **4**: 326–41.

9 Muthigi A, George AK, Sidana A *et al.* Missing the mark: prostate cancer upgrading by systematic biopsy over magnetic resonance imaging/transrectal ultrasound fusion biopsy. *J. Urol.* 2017; **197**: 327–34.

10 Moldovan P, Udrescu C, Ravier E *et al.* Accuracy of elastic fusion of prostate magnetic resonance and transrectal ultrasound images under routine conditions: a prospective multi-operator study. *PLoS ONE* 2016; **11**: e0169120.

11 Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* 2004; **240**: 205–13.

12 Bossuyt PM, Reitsma JB, Bruns DE *et al.*; For the STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; **351**: h5527.

13 Barentsz JO, Richenberg J, Clements R *et al.* ESUR prostate MR guidelines 2012. *Eur. Radiol.* 2012; **22**: 746–57.

14 Barentz JO, Weinreh JC, Verma S *et al.* Synopsis of the PI-RADS v2 guidelines for multiparametric prostate magnetic resonance imaging and recommendations for use. *Eur. Urol.* 2016; **69**: 41–9.

15 van den Bergh RC, Roemeling S, Roobol MJ *et al.* Prospective validation of active surveillance in prostate cancer: the PRIAS study. *Eur. Urol.* 2007; **52**: 1560–3.

16 Mozer P, Rouprêt M, Le Cossec 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**: 50–7.

17 Peltier A, Aoun F, Lemort M, Kwizera F, Paesmans M, Van Velthoven R. MRI-targeted biopsies versus systematic transrectal ultrasound guided biopsies for the diagnosis of localized prostate cancer in Biopsy Naive Men. *Biomed. Res. Int.* 2015; **201**: 1–6.

18 Ukimura O, Gross ME, de Castro Abreu AL *et al.* A novel technique using three-dimensionally documented biopsy mapping allows precise re-visiting of prostate cancer foci with serial surveillance of cell cycle progression gene panel. *Prostate* 2015; **75**: 863–71.

19 Delongchamps NB, Peyromaure M, Schull A *et al.* Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. *J. Urol.* 2013; **189**: 493–9.

20 Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. *Urology* 2013; **81**: 1372–8.

21 Portalez D, Mozer P, Cornud F *et al.* Validation of the European Society of Urogenital Radiology scoring system for prostate cancer diagnosis on

multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. *Eur. Urol.* 2012; **62**: 986–96.
22 Baco E, Rud E, Eri LM *et al.* A randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy. *Eur. Urol.* 2016; **69**: 149–56.
23 Siddiqui MM, Rais-Baharami SS, Turkbey B *et al. JAMA* 2015; **313**: 390–7.
24 Moore CM, Robertson NL, Arsanious N *et al.* Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. *Eur. Urol.* 2013; **63**: 125–40.
25 Bastian-Jordan M. Magnetic resonance imaging of the prostate and targeted biopsy, Comparison of PIRADS and Gleason grading. *J. Med. Imaging Radiat. Oncol.* 2017; https://doi.org/10.1111/1754-9485.12678.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. PCa detection according to PI-RADS score version 1.0 or 2.0.

Table S1. Biopsy results in terms of PCa and clinically significant PCa detection, comparing target biopsies only with target + random biopsies, stratified as per PI-RADS version 1.0 and 2.0.