Evolution of prostate cancer diagnosis: retrospective analysis of magnetic resonance imaging/ultrasound fusion guided biopsies protocol in routine practice and patients management

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Background: Magnetic resonance imaging (MRI) is today strongly recommended in prostate cancer (PCa) diagnosis. Therefore, MRI/ultrasound (MRI/US) fusion-guided biopsy is becoming the new standard patients management.

Methods: We report our experience during the last 4 years using this technique, with a protocol of 6 random cores (instead of the most used 12 cores protocol) associated to the target cores (2 to 3 per lesion). Our study involved 236 patients including real life routine practice: biopsy naïve patients (n=107), patients with previous negative standard prostate biopsies (n=67) and patients in PCa active surveillance (n=62). Finally, 76 patients have a robotic radical prostatectomy.

Results: Mean age of the population was 66 years. Median PSA was 8.5 ng/mL. Overall and significant cancer detection were respectively 66.6% and 38.5%, with a large difference considering biopsy history: 63.5% in biopsy naïve patient, 53.7% in patient with previous negative biopsies and 82.3% in patients under active surveillance. Targeted biopsies missed 28 cancers among 8 were significant and standard biopsies missed 33 cancers among 14 were significant. Moreover, concordance between biopsy samples and radical prostatectomy specimens was evaluated at 80%.

Conclusions: Comparing to literature data, similar results were observed in our retrospective study, even with reduced random cores, suggesting a real change in patients management in particular in active surveillance group with a reclassification rate of 56.4% using the Epstein criteria.

Keywords: Prostate cancer (PCa); magnetic resonance imaging/ultrasound fusion-guided biopsy (MRI/US fusion-guided biopsy)

Introduction

Despite transrectal ultrasound guided systematic prostate biopsy is the standard-of-care in diagnosis of prostate cancer (PCa), it has poor diagnostic accuracy for PCa detection (1). It may fail to detect the presence of cancer due its low sensitivity and specificity (2), so that the false-negative rate may reach 50% (3). Furthermore, 30% of aggressive tumors are usually misdiagnosed (4).

The ability to detect PCa on magnetic resonance imaging (MRI), using different prognostic scores and systems (PI-

RADS) has led to the development of three MRI-guided prostate biopsy methods: cognitive fusion biopsy, MRI/ultrasound (MRI/US) fusion-guided biopsy and biopsy performed in gantry in an MRI suite (5). As the first one lacks of precision and depends on the operator's expertise, and the third one is still expensive at the moment, MRI/US fusion biopsy is being embraced as the new standard technique (6). Nevertheless, there is no consensus for the moment about the optimal protocol of biopsies to perform in PCa initial diagnosis.

The objective of this retrospective study was to report the results of our experience in real life routine practice using the MRI/ultrasound imaging biopsy technique with 6 random cores associated to targeted cores (2 to 3 per lesion), with comparison to the main publications of the literature.

Methods

In this retrospective study, we reported our experience of MRI/US fusion biopsy in an academic reference urological center, during a 4 years period from September 2015 to May 2019.

There were no exclusion criteria based on age, PSA, prostate volume, previous history of prostate biopsy. All patients have at least one suspicious lesion on multiparametric MRI (mp-MRI).

Subsequently to fusion biopsy, histological results of radical prostatectomy specimens were also analyzed. An ethical waiver was applicable as the study was a retrospective service evaluation without any change in patient management.

Multiparametric MRI

A mp-MRI was performed for all patients, including T2-weighted imaging (T2w), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced (DCE) imaging. All MRIs data were reviewed by a single referring uro-radiologist (M Lair), and suspicious lesions were scored according to the PI-RADS classification (version 2) (7).

Biopsies procedure

Fusion biopsies were performed with the UroStation™ (Koelis, Grenoble, France). Suspect lesions (PI-RADS ≥3) were previously contoured and recorded by our radiologist

(M Lair). All procedures were performed under local anesthesia, by two urologists experienced in PCa. During the procedure, we always realized 2 to 3 targeted biopsies on each suspect lesion associated to a sextant scheme of six random biopsies (one core, bilaterally from each base, mid and apex).

All biopsies and prostatectomy specimens after radical prostatectomy were analyzed by an experienced uro-pathologist (F Gobet). To date, there is always a debate about the definition of significant PCa. Anyway, we considered EAU guidelines definition of a PCa with a Gleason 7 or higher score (1).

Statistical analysis

Descriptive statistics were performed to summarize clinical, MRI data, fusion biopsy samples and prostatectomy specimens' characteristics. Spearman correlation coefficient was performed to assess the Gleason's score concordance between fusion biopsy samples and prostatectomy specimens.

Results

A total of 244 patients with MRI/US fusion prostate biopsy were reported during the study period. During the same period, 444 standard prostate biopsies were realized in our department. The interest of *Figure 1* was to underline the evolution of the two biopsies techniques during the study period. Eight patients were excluded from the analysis because they had only targeted biopsies without random ones associated.

In real life routine practice, we stratified the included 236 patients into 3 groups: 107 biopsy naïve patients, 67 patients with previous negative standard prostate biopsies and 62 patients under PCa active surveillance.

The general characteristics of the patients and mp-MRI features are shown in *Table 1*. Mean age of the patients was 66 years (48 to 84). Median PSA was 8.5 ng/mL. Only 26 patients had an abnormal digital rectal exam. According to MRI data, median prostate volume was 62 cm³. A single lesion was noticed in 192 (81.4%) cases and 44 (18.6%) patients had two or more lesions. A total of 294 suspects mp-MRI lesions were described: 62 PI-RADS 3 lesions (21%), 154 PI-RADS 4 lesions (52.50%), and 78 PI-RADS 5 lesions (26.5%). Mean size of lesions was 12.5 mm. A mean of 4.9 (2 to 12) targeted biopsies were carried out per patient. Biopsy and radical prostatectomy outcomes

Figure 1 Monthly evolution of the number of standard and fusion biopsies during the study.

Table 1 Patients characteristics and mpMRI features

Parameters	Values
Men included (all n=244)	236
Mean age (years) [range]	66 [48–84]
Mean PSA (ng/mL) [range]	8.5 [0.5–80]
Mean prostate volume (cc) [range]	62 [15–270]
Family history of prostate cancer, n (%)	26 (11.0)
Abnormal digital rectal examination, n (%)	26 (11.0)
Biopsies history, n (%)	
Biopsy naïve	107 (45.3)
Previous negative biopsies	67 (28.4)
Patients in active surveillance	62 (26.3)
PI-RADS targets (maximum score in case of multiple targets), n (%)	
PI-RADS 3	38 (16.1)
PI-RADS 4	125 (53.0)
PI-RADS 5	73 (30.9)
Number of biopsy cores	
Standard	1,418
Targeted	1,160
Mean of targeted biopsies per patient [range]	4.9 [2–12]
mpMRI targets per patient	
Single	192
Multiple	44
Mean [range] size of targets (mm)	12.5 [3–30]

are reported in *Table 2*. The overall cancer detection rate (CDR) was 66.6%, and down to 38.5% if only considering clinically significant cancer.

As shown in the *Figure 2*, the PI-RADS score was associated with the presence of PCa as 84.7%, 64% and 34.2% of respectively PI-RADS 5, PI-RADS 4 and PI-RADS 3 lesions biopsies were positive, as well as the presence of significant PCa (respectively 64.3%, 32% and 10.5%). PCa was detected only in random and targeted biopsies respectively in 28 (18%) and 33 (21.3%) cases. It was detected in both biopsies in 94 (60.6%) cases. Targeted biopsies missed 28 cancers among 8 were significant and standard biopsies missed 33 cancers 14 were significant (*Figure 3*).

CDR was widely different depending on the patient history. Therefore, CDR was 63.5% in biopsy naïve patient, 53.7% in patient with previous negative biopsies and 82.3% in patients in active surveillance. When considering significant cancer definition, biopsy naïve and active surveillance groups toward to have similar CDR (42.9% and 43.5% respectively), as patient with previous negative biopsies have lower but none negligible CDR (25.3%).

Among the 62 patients in active surveillance and in consideration with Epstein Criteria, 35 (56.4%) were eligible to an active treatment after undergoing fusion biopsy. Robot-assisted radical prostatectomy was performed in 76 men. Considering the whole Gleason score, concordance between biopsy samples and radical prostatectomy specimens was 80% (*Figure 4*). The Spearman correlation coefficient showed a very strong and

Table 2 Biopsy and prostatectomy histological results

Parameters	Values
Patients with prostate cancer, n (%)	155 (65.7)
On targeted biopsy only	33 (14.0)
On random biospy only	28 (11.9)
On both biopsy	94 (39.8)
Patients with significant prostate cancer, n (%)	90 (38.1)
On targeted biopsy only	14 (5.9)
On random biospy only	8 (3.4)
On both biopsy	68 (28.8)
Overall cancer detection rate, n (%)	155 (65.7)
Biopsy naïve	68/107 (63.5)
Previous negative biopsies	36/67 (53.7)
Patients in active surveillance	51/62 (82.3)
Significant cancer detection rate, n (%)	90 (38.1)
Biopsy naïve	46/107 (43.0)
Previous negative biopsies	17/67 (25.4)
Patients in active surveillance	27/62 (43.5)
Robot-assisted radical prostatectomy	76
Gleason score concordance between fusion biopsy samples between radical prostatectomy specimen	60/76 (78.9)
Gleason 6 reclassement from biopsy to radical prostatectomy specimen	11/25 (44.0)
Non eligible men to active surveillance after fusion biopsy according to Epstein criteria	35/62 (56.5)
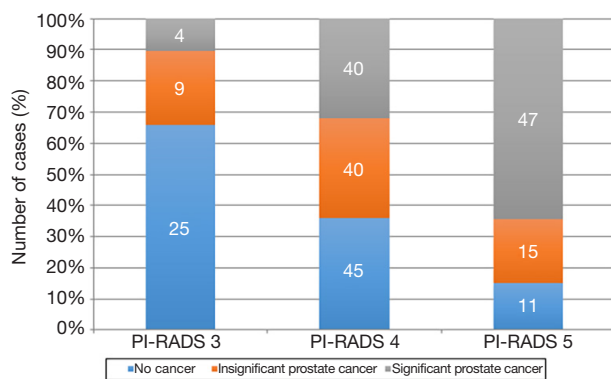
Figure 2 Overall PCa and significant PCa detection rate according to PI-RADS score.
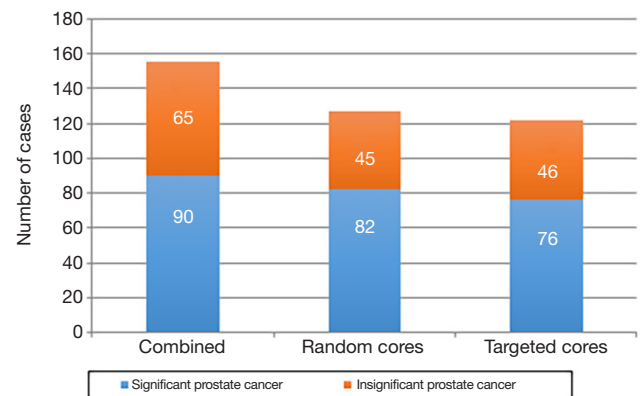
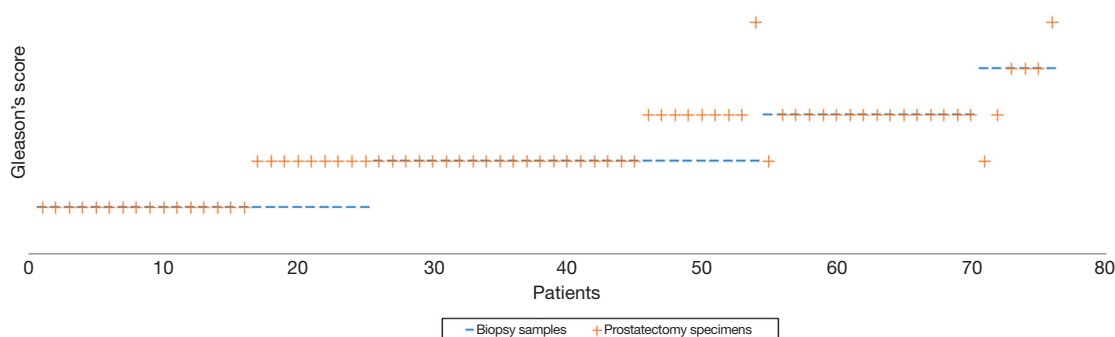**Figure 3** PCa detection according to the combined and separated biopsy.

Figure 4 Concordance of Gleason score between biopsy samples and prostatectomy specimens.

significant positive correlation between the two histological scores (P=0.81, P<0.001). As regarding patients with Gleason 6 on biopsies samples, 44% were upgraded to Gleason 7 or higher on radical prostatectomy specimen.

Discussion

In our retrospective study, overall CDR was 63.5%, which were slightly higher than other fusion biopsies studies data (8,9). This is probably related to the heterogeneity of the study population with an important group of PCa patients already diagnosed and under active surveillance. In fact, across studies, PCa detection rate was variable and was influenced by patient selection study designs and reporting which made difficult a head-to head comparison.

In the early 2000's, saturation biopsies were proposed to patients with previous negative biopsies but raising PSA and clinical suspicion for PCa. More recently, the advent of multiparametric MRI permits to identify suspicious prostate lesions with a high accuracy. Different MRI classification scores were validated to objectively grade those suspicious lesions. PI-RADS (version 2) remains today the most used in clinical practice, with the advantage, in plus of its accuracy, to present an overall good inter-observer agreement among radiologists with different levels of experience (10). These radiological data suggest to proposed biopsies targeting directly suspicious lesions, rather than repeated systematic biopsy. As reported by Sonn *et al.* fusion biopsy provides improved detection of PCa in men with prior negative biopsies with an overall CDR of 34% (11). Anyway, the reported CDR for significant PCa in men with a prior negative biopsy can range between 20 and 40% and is lower compared to detection rate in biopsy-naive patients (12,13).

Different series have evaluated the interest of performing targeted biopsies in primary intention for naïve patients. Mozer *et al.*, in a series of 152 patients with a control arm of conventional echo-guided biopsies, concluded that biopsies targeted with Urostation (Koelis®) have detected a lower number of cancers at all grades (54% *vs.* 57%), but more lesions clinically significant (43.4% *vs.* 36.8%) (14). Similar results have been reported by Pokorny *et al.* with a higher high-risk carcinoma rate in the targeted biopsy group (65.5% *vs.* 52.1%) (15). Using another software (Virtual Navigator), Delongchamps *et al.* observed a significantly higher CDR (82.1% *vs.* 45.8%), with a higher Gleason score 7 rate than in the targeted biopsy group (16). A recent international study, PROMIS, has underlined that performing an initial selection of patients by MRI before any biopsy could potentially avoid the practice of biopsies in 27% of patients, and would guide the subsequent biopsy for patient with suspicious lesions (17). Anyway, these literature data are similar to our retrospective study showing a CDR at biopsy naïve men of 63.5%, clinically significant in 42.9%.

In contrast, in active surveillance the reclassification rate was much lower, ranging from 2.5% for Soloway *et al.* (18), up to 22% for Berglund *et al.* (19). Therefore, those findings would indicate mp-MRI and targeted biopsy at initial evaluation during an active surveillance protocol to offer more relevant detection of significant cancers (20). On a series of 113 patients, Hu *et al.* noted a reclassification rate of 36% according to the Epstein criteria (Gleason score less than 7, invasion of less than 3 cores and/or tumor extent less than 50% per carrot) (21). Using the same criteria, reclassification rate in our study would be 56.4%. Nahar *et al.* showed that targeted biopsies made 33% of patient ineligible to active surveillance considering Epstein criteria (22). Half of those patients were ineligible because of Gleason upgrading.

Should we systematically combine standard biopsies with targeted biopsies in routine practice? From a morbidity point of view, no series has shown a significant decrease of complications by reducing the number of samples. Nevertheless, the number of samples seems to be correlate with less patient pain. Siddiqui *et al.* observed the same detection rate for overall prostate carcinoma between standard biopsies and targeted biopsies, but the latter allowed diagnosing 30% of high-risk tumors and 17% fewer tumors low risk (23). Our results are also in concordance with the literature data. Rouvière *et al.* in the "MRI-First" study concluded that significant CDR was improved by combining both techniques and both techniques showed substantial added value (24). In our experience, only 8% of significant cancers were diagnosed on randomized samples. Many studies have reported that the percentage of clinically significant cancer missed by fusion biopsy, but detected by standard biopsy could reach to 10% (23,25). Such data clearly confirm the necessity of combining target and random biopsies.

Recently, Aminsharifi *et al.* have evaluated the six random cores protocol and showed an increased efficiency of detecting clinically-significant PCa even with fewer random cores (26). Siddiqui *et al.* reported that performing exclusively targeted biopsies allowed diagnosis of the same rate of PCa as combined biopsies, with higher significant cancer rates, and fewer samples (57%) (27). As well, the randomized PRECISION study compared two groups of biopsy naïve men: the MRI-targeted biopsy group (without random biopsy cores) versus standard biopsy group. They concluded that even if targeted biopsy alone misses a low rate of significant cancer, this procedure remains superior to standard biopsy, with the diagnosis of more significant cancer and fewer insignificant cancer (28).

Concerning surgery outcomes, Velez *et al.* reported their histological results on patients who had radical prostatectomy after fusion biopsy (29). Gleason scores were unchanged in 71% of cases with a Spearman correlation coefficient of 0.75, which is comparable to our study results. Bloom *et al.* reported a rate of 44% of upgrade among their 466 Gleason 6 patients (25). In the other hand, some studies concluded that MRI/US biopsy besides their higher significant PCa detection rate comparing to standard biopsy, have also less upgrading of cancers at surgery (30,31).

Conclusions

In conclusion, targeted biopsies led to increase clinically

significant CDR, which has been consistently reported across cohort studies despite wide variations in MRI protocols, patient selection and operator technique. In our series, CDR was 63.5% in biopsy naïve patient, 53.7% in patient with previous negative biopsies and 82.3% in patients in active surveillance. Moreover, targeted prostate biopsy is tending to become the gold standard in the management of patients with PCa suspicion. Our study demonstrated in comparison with literature data that a reduced number of random cores could be associated with similar results, suggesting a real change in patient's management in particular in active surveillance group. Using the Epstein criteria, reclassification rate in our study would be 56.4%.

Acknowledgments

Footnote

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