The Detection of Prostate Cancer with MRI-targeted Prostate Biopsies is superior with the Transperineal than the Transrectal Approach. An EAU-YAU Prostate Cancer Working Group Multi-Institutional Study.

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COMPLIANCE WITH ETHICAL STANDARD

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All included patients undergoing radical treatment provided written informed consent for surgery. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional review board apply to each centers due to observational and retrospective nature of the study.

Abstract

Purpose: to evaluate whether transperineal MRI-targeted prostate biopsy (TP-TBx) may improve the detection of clinically significant prostate cancer (csPCa) defined as ISUP≥2, in comparison to transrectal MRI-targeted prostate biopsy (TR-TBx).

Materials & methods: A multicenter retrospective cohort study comprising patients who underwent MRI guided prostate biopsy was conducted. To address possible benefits of TP in the detection of prostate cancer (PCa) and csPCa, a cohort of patients undergoing TP-TBx were compared to patients undergoing TR-TBx. Multivariable logistic regression analysis were performed to assess predictors of PCa and csPCa detection.

Results: Overall, 1,936 and 3,305 patients who underwent TR vs.TP MRI-targeted biopsies at 10 referral centers were enrolled. The rate of PCa and csPCa diagnosed was higher for TP-TBx vs. TR-TBx (64.0% vs. 50%,p<0.01 and 49% vs. 35%,p<0.01). At multivariable analysis adjusted for age, biopsy naïve/repeated biopsy, cT stage, PI-RADS, prostate volume, PSA and number of biopsy cores targeted, TP-TBx was an independent predictor of PCa (odds ratio (OR) 1.37,95% CI 1.08-1.72) and csPCa (1.19,95% CI 1.12-1.50). When considering the approach according to the site of the index lesion, TP-TBx had a significantly higher likelihood than TR-TBx to detect csPCa in the apex (OR 4.81, 95% CI 1.03-6.27), transition/central zone (OR 2.67,95% CI 1.42-5.00) and anterior zone (OR 5.62,95% CI 1.74-8.13).

Conclusions: The use of TP-TBx allows a better cancer grade definition and Pca risk assessment. This has important implication in the decision-making process and in patients counseling for further therapies.

Introduction

Over the last few years, the introduction of multiparametric MRI (mpMRI) altered the diagnostic pathway of prostate cancer (PCa), where the use of MRI-targeted biopsies (TBx) is now recommended by several guidelines including those of the European Association of Urology (EAU). Prostate biopsies can be performed by different approaches such as transrectal targeted biopsy (TR-TBx) or transperineal targeted biopsy (TP-TBx). In addition, MRI-targeted biopsies (either via TR or TP) can be performed by means of cognitive-targeted biopsy (cognitive-TBx) or mpMRI-TRUS fusion biopsy (fusion-TBx) with an overall improvement in the detection rates of clinically significant prostate cancer (PCa) compared to conventional TRUS systematic biopsies [1]. Interestingly, there is no clear superiority of one approach over the other [2] and no robust randomized control trials has been completed to address this issue. Although clinical guidelines recently changed and currently recommend the use of TP-Bx over TR-Bx due to the reduced risk of side effects and infectious events, the debate on the superiority of one approach over the other in terms of deliverability in the outpatient setting, accessibility in the prostate gland and location of the tumor and the reproducibility of the technique is still open [3,4]. Indeed, one of the potential advantages of the TP approach is to allow an easier access to certain prostate zones including the anterior zone and the apical and dorsolateral horns, which may be under-sampled using the TR route [5,6]. Interestingly, although there is robust evidence that biopsies performed with TR-TBx may reduce the risk of misclassification of PCa in men with MRI-visible lesions [7], the comparison of detection rates of significant cancer between TP-TBx and TR-TBx has been poorly reported so far [8]. Only limited data available suggest that TP-TBx is as good as systematic template TP biopsy [9,10] and that the TP approach may confer an advantage for detecting anterior tumors [11], even in the MRI- targeted era. Furthermore discordant data have been reported regarding the optimal technique, namely

cognitive-TBx vs fusion-TBx [12,13]. Moreover, there are no head-to-head studies comparing the different MRI-targeted methods (cognitive-TBx vs fusion-TBx) within TP biopsies (brachytherapy grid VS freehand technique).

In the face of such a paucity of data, our aim was to evaluate whether TP-TBx may improve the detection of csPCa in comparison to TR-TBx, to assess whether the detection rates of the two approaches vary according to the index lesion and to evaluate which is the best target approach (fusion vs. cognitive).

Materials & methods:

A total of 5241 patients from 10 tertiary referral centers were included. Internal Review Board approval for the present study and for retrospective data collection was obtained according to each institution's policy. Written informed consent from the study participants was obtained in each centers. A multiparametric MRI was performed according to each institution protocol. MRI were scored in most centers by the PIRADSv2 scoring system[NO_PRINTED_FORM]All MRIs were reviewed in each center by expert genitourinary radiologists according to ESUR/ESUI consensus for the quality requirements for image acquisition, interpretation and radiologists' training. All consecutive positive and negative TBx performed by experienced urologists with more than 100 cases [14] with their preferred biopsy approach (TR or TP) were retrospectively collected. TP-TBx was performed with brachytherapy grid or freehand technique, including a fusion (TP-fusion-TBx) or cognitive technique (TP-cognitive-TBx) under general or local anesthesia. A median number of 3 (Q1-Q3: 2-4, IQR:2) target biopsy samples were taken from each suspicious lesion. Patients with previous treatment for PCa were excluded. If patients had undergone previous prostate biopsies or in active surveillance, only the last biopsy was considered in this study.

A computerized databank was gathered for data transfer of anonymized patients. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems.

Covariates and outcomes

Clinically significant PCa (csPCa) was defined as ISUP ≥2 group. The detection of PCa and of csPCa were evaluated considering exclusively the results of MRI-targeted biopsy and concomitant systematic cores were not evaluated.

Statistical analysis

Categorical variables were reported as frequencies, while continuous variables were reported as median, quartiles and interquartile range (IQR). Differences between categorical variables were assessed by using chi-square test. Differences between continuous variables were assessed by T-test or Mann-Whitney test, as appropriate. Multivariable logistic regression analysis for predictors of PCa and csPCa were performed to evaluate the odds ratio (OR) for TP-TBx and TR-TBx. The model was adjusted for pre-selected variables as: age, biopsy set (biopsy naïve/repeated biopsy), cT stage (cT≥2 vs cT<2), PI-RADS, prostate volume, PSA and number of biopsy cores targeted. Sensitivity analyses were performed after stratifying patients according to the index lesion tumor location (mid/base, apex, peripheral zone, transition/central zone) and different TP biopsy approach (brachytherapy grid vs. freehand technique) and MRI-targeted methods (cognitive-TBx vs. fusion-TBx). Significance for all tests was set at $p< 0.05$. Analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA).

Results:

From December 2014 to November 2020, 10 centers (7 from Europe, 2 from China and 1 from Australia) participated to the study. A total of 1,936 TR-TBx and 3,307 TP-TBx were included. Table 1 lists the general demographics and patients' characteristics of the two prostate biopsies groups. All TR-TBx biopsies used a dedicated biopsy fusion software while TP-TBx were performed with a fusion software or with a cognitive technique respectively in 69.2% and 30.8%. TP biopsies with a brachytherapy grid and with a freehand technique were performed respectively in 42% and 58%. Baseline characteristics differ between groups for PI-RADS distribution, prostate volume and tumor location.

Overall, PCa and csPCa were more frequent in the TP-TBx in comparison to TR-TBx (respectively 64% vs 50% for PCa and 49% vs 35% for csPCa; p<0.01). At multivariable analysis, TP-TBx was associated with higher risk of PCa compared to TR-TBx (OR 1.37, 95% CI 1.1-1.7, p<0.01) and csPCa (1.2, 95% CI 1.1-1.5, p=0.04), once adjusted for covariates (table 2). Similar results were obtained in a sub-analysis including only fusion software TP-TBx and TR-TBx (supp table 1).

When stratifying patients according to the index lesion location, TP-TBx was associated with higher risk of PCa compared to TR-TBx to detect PCa at the peripheral zone (OR: 1.4, 95% CI: 1.1-1.9, p=0.02), transition/central zone (OR 2.1, 95% CI 1.3-3.3; p<0.01), and anterior zone (OR 2.4, 95% CI 1.0-6.5, p=0.045). Of note, TP-TBx was associated with higher risk of PCa compared to TR-TBx of csPCa at the apex (OR 4.8, 95% CI 1.0-6.3, p=0.04), transition/central zone (OR 2.7, 95% CI 1.4-5.0, p<0.01) and anterior zone (OR 5.6, 95% CI 1.7-8.1, p=0.04) (supp. table 2-6).

In a sub-analysis of only TP biopsies (table 3), fusion-TBx compared to cognitive TBx was not found to be an independent predictor of PCa (OR 0.9, 95%CI: 0.8-1.0; p=0.1) and csPCa (OR 0.9, 95%CI: 0.8-1.0; p=0.1). Finally, TP-TBx with brachytherapy grid vs freehand TP-TBx technique were found to be independent predictors of PCa (OR 1.5, 95%CI: 1.2-2.0, p<0.01 but not of csPCa(OR 1.2, 95%CI: 0.9-1.5; p=0.1) when adjusted for covariates .

Discussion

The interest towards the TP approach remains high not only in terms of complications but also in terms of ability to define the exact cancer localization especially those who are clinically significant. No differences between TP and TR routes for PCa detection were shown on random biopsies [15]; however, these findings may not be transferable to a TBx context. In the present paper we report a multi-institutional experience in the detection of PCa and csPCa with TR or TP TBx.

Our results are several-fold. First, our analyses in a large cohort from referral centers demonstrated that TP-TBx might be characterized by a higher detection of PCa and, more importantly, of csPCa than fusion TR-TBx. This is in line with small retrospective single institutional experiences. For example, in a non-inferiority study by Ber et al. the accuracy of TP-fusion-TBx was compared to TR-fusion-TBx in 77 patients [16]. Participants were randomized to TP-fusion followed by a TR-fusion, or vice-versa. TP-fusion biopsies were not inferior and superior in detecting csPCa within MRI-visible index lesion. Absolute difference for csPCa diagnosis was 15.6 (CI 95% 3.2-27.9%) in favor of TP-fusion (p=0.029). Pepe et al. compared TR-TBx to TP-TBx in the re-biopsy setting [17]. Men who had a suspicious lesion on mpMRI (PI-RADS 4 or 5) underwent both TR-TBx using fusion software and TP-TBx using cognitive fusion followed by saturation TP biopsy during the same procedure. Using saturation biopsy as the reference standard, csPCa was found in 60 cases (30%) among all of them were detected on mpMRI. In particular, PCa detection rates within all the prostate gland and disease located in the anterior zone was higher for the TP-TBx in comparison to the TR-TBx. A higher cancer detection of TP-TBx than TR-TBx has been suggested, especially for cancers involving the anterior zone of the gland [17-20]. The added value of the TP-TBx in comparison to the TR-TBx has also been reported by a recent systematic review. This study showed that the detection rates of csPCa with TP-TBx for anterior tumors were statistically significantly higher (relative risk 2.46 95% CI 1.22–4.98],

p=0.01) on a per-lesion analysis (defined as the proportion of MRI significant lesions that are also biopsy-positive clinically significant lesions). However, as a major limitation of the review, all outcomes measured in each included study has a "very low" certainty of evidence according to the GRADE evaluation [18].

Second, no large multicenter series assessed whether the TP route may improve csPCa detection in the MRI era with special attention to the location of the tumor. In particular, TP-TBx showed some advantages in certain aspects of the gland, namely the apex, the transition/central zone and the anterior zone. These results significantly add some points in favor to MRI diagnostic pathway which has been critically analyzed by some authors [19,20]. Indeed, several significant cancers mostly located in the anterior portion of the gland were missed by TR-TBx. In a study by Schouten et al., TR-TBx did miss a non-negligible number of significant cancers (approx. 7% at patient-level and 35% at segment-level analysis) that were mainly located at the apex and in dorsolateral regions [6]. The diagnostic advantages of TP biopsies compared to TR can be explained by the largest diameter of most prostate tumors along the longitudinal axis (apex to base) [21]. The TP needle is inserted along the same axis. Contrarily, in TR biopsies the needle penetrates through anterior–posterior axis and thus even targeted biopsies are centered on a narrower axis. Sampling larger tumor volume may also improve detection of higher grade tumors, reducing sampling errors associated with tumor heterogeneity [22]. As a consequence, a higher detection of tumors in the apex results in a better surgical and radiotherapy pretreatment assessment with possible implications in the functional and oncological outcomes.

Third, multiple studies report no clear differences in cancer detection rates between visual estimation and image-fusion, despite differences in biopsy protocol and image fusion platform between studies [2,23]. The diagnostic ability of fusion biopsy and visually directed targeted biopsy seem almost comparable in the literature [13,24]. A major limitation of these studies was the need to perform first the fusion-TBx to achieve acceptable matching

between MRI and ultrasound in the same patient [24]. Furthermore, if only larger lesions were biopsied, this may have negatively affected the potential of MRI-TBx. Thus, a possible bias in favor of cognitive-TBx cannot be excluded. However, also in our study the diagnostic ability of TP-fusion-TBx and TP-cognitive TBx seems to be equivalent of the software-based strategy.

Finally, when different targeted biopsy techniques were compared within TP biopsies, the use of a brachytherapy grid is not a predictor of the detection of csPCa. These results could have important implications in further diffusion of TP biopsies as a procedure easily performed with reduced anesthesia needs, minimal risk of sepsis, reduced risk of urinary retention [25] and more freedom of movements [26].

We recognize the limitations to make meaningful comparisons of diagnostic accuracy between biopsy techniques in a study of this size that is conducted retrospectively. Indeed, there is a wide array of biopsy options available to compare (different biopsy techniques, software used for the fusion biopsies, number of targeted biopsies) as well as the different clinical settings in which they were used. Specifically, it comprised both biopsy-naïve and prior negative-biopsy patients submitted to different techniques without any randomization, and thus there is a risk of selection bias.

Different baseline characteristics between groups may have irrelevant clinical impact however a selection bias could not be excluded. For instance, the significantly small size of prostates in TP Vs TR biopsies could have contributed to the higher PCa detection rate in the TP approach, although the PSA density is comparable between the two groups. More needle deployments are invoked in the TP approach, resulting in a possible lower sampling efficiency and higher detection rates, although analyses were adjusted for the n. of cores taken. Number of targeted cores has slight variation between the two groups. As also showed by other authors [27] an increasing number of targeted cores increases detection of cancers, however the addition of only one core in a multiple set of fusion biopsies have

limited impact. We recognize that ideally targeted cores should have been constant however, there is a linear correlation between the number of cores and the prostate volume for the two groups. This can be the expression of common clinical practice between centers and similar internal protocols since the optimal number of prostate biopsy cores for each MRI index lesion remains controversial. This may be partly a result of various MRI targeted biopsy techniques (MRI US software fusion, cognitive fusion), the indication for the biopsy (biopsy-naïve, prior negative biopsy, prior cancer diagnosis), and the tumor characteristics (homogeneity and heterogeneity) [27,28]. It would seem that transperineal approach might be associated with more mature use of MRI due to its increasing use. However, in the present series the majority of data are from biopsies performed in the last 2 years for both groups.

The advent of targeted prostate biopsies to suspicious lesions based on imaging confers to an improved detection of clinically significant prostate cancer with a possible inflation of the ISUP grade. In the present series, patients may be upgraded by focusing the sampling at areas of high-grade cancer found at mpMRI in particular, for those regions better biopsied with TP approach [29]. The oversampling of these lesions is likely to better represent the cancer grade. However, such grade increase might lead to the Will Rogers phenomenon. For this reason, this higher rate should be interpreted with care. Some detected cancers may correspond to small cancers as a result of stage/grade migration, while others may be aggressive tumors that would otherwise have been missed. In addition, targeted biopsy cores through the MRI-visible parts of lesions may lead to more over- grading when compared to standard biopsy approaches [30].

With all these limitations, the results from this study still represent real clinical practice and therefore must be considered generalizable.

Although images and the final pathologies were not centrally reviewed, our results apply to experienced centers where both TP-TBx and TR-TBx are performed routinely.

Conclusion

In the current standard practice of MRI-targeted biopsies, TP-TBx improve csPCa detection compared to TR-TBx, especially in the apex, transition/central zone and anterior zones. This has potential implications in the Pca risk assessment, patients counseling and planning for further therapies. The outpatient setting for TP-TBx is an excellent option since: 1) software based TP-TBx does not offer a clear advantages compared to cognitive fusion biopsies; 2) freehand TP-TBx allows similar results for csPCa compared to grid-guided TP-TBx.

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