TOPIC PAPER

Refining the risk-stratification of transrectal biopsy-detected prostate cancer by elastic fusion registration transperineal biopsies

Bertrand Covin[1] · Mathieu Roumiguié[1] · Marie-Laure Quintyn-Ranty[2] · Pierre Graff[3] · Jonathan Khalifa[3] ·
Richard Aziza[4] · Guillaume Ploussard[1] · Daniel Portalez[4] · Bernard Malavaud[1]

Abstract

Purpose To evaluate image-guided Transperineal Elastic-Registration biopsy (TPER-B) in the risk-stratification of low–intermediate risk prostate cancer detected by Transrectal-ultrasound biopsy (TRUS-B) when estimates of cancer grade and volume discorded with multiparametric Magnetic Resonance Imaging (MRI).

Methods All patients referred for active surveillance or organ-conservative management were collegially reviewed for consistency between TRUS-B results and MRI. Image-guided TPER-B of the index target (IT) defined as the largest Prostate Imaging-Reporting Data System-v2 ≥ 3 abnormality was organized for discordant cases. Pathology reported Gleason grade, maximum cancer core length (MCCL) and total CCL (TCCL).

Results Of 237 prostate cancer patients (1–4/2018), 30 were required TPER-B for risk-stratification. Eight cores were obtained [Median and IQR: 8 (6–9)] including six (IQR: 4–6) in the IT. TPER-B of the IT yielded longer MCCL [Mean and (95%CI): 6.9 (5.0–8.8) vs. 2.6 mm (1.9–3.3), $p < 0.0001$] and TCCL [19.7 (11.6–27.8) vs. 3.6 mm (2.6–4.5), $p = 0.0002$] than TRUS-B of the gland. On TPER-B cores, longer MCCL [Mean and (95%CI): 8.7 mm (6.7–10.7) vs. 4.1 mm (0.6–7.6), $p = 0.002$] were measured in Gleason score-7 cancers. TPER-B cores upgraded 13/30 (43.3%) patients. 14/30 (46.7%) met University College London-definition 1 and 18/30 (60.0%) definition 2, which correlate with clinically significant cancers > 0.5 mL and > 0.2 mL, respectively. 7/16 (43.8%) patients under active surveillance were re-allocated toward prostatectomy ($n = 5$) or radiation therapy ($n = 2$). In 14 patients not yet assigned, TPER-B risk-stratification spurred the selection (13/14, 92.9%) of treatments with curative intent.

Conclusion Image-guided TPER-B of the index target provided more cancer material for pathology. Subsequent re-evaluation of cancer volume and grade switched a majority of patients towards higher-risk groups and treatments with curative intent.

Keywords Prostatic Neoplasms · Endoscopy · Diagnostic imaging · Biopsy

✉ Bernard Malavaud
bernard.malavaud@me.com

1   Department of Urology, Institut Universitaire du Cancer, Toulouse, France

2   Department of Pathology, Institut Universitaire du Cancer, Toulouse, France

3   Department of Radiation Oncology, Institut Universitaire du Cancer, Toulouse, France

4   Department of Radiology, Institut Universitaire du Cancer, Toulouse, France

Introduction

Standard of care transrectal ultra-sound-guided biopsy (TRUS-B) [1] and "quantitative biopsy pathology" (Gleason score, highest Gleason grade, cancer core length or percent) [2] are instrumental in the estimation of clinically relevant risks, such as biochemical recurrence after primary treatment [1] or prostate cancer-specific mortality [3].

By informing targeted biopsies, multiparametric Magnetic Resonance Imaging (MRI) was shown to highlight clinically significant cancer better than standard TRUS-B [4] and to facilitate the characterization of the index tumor [5, 6]. However, its position in risk-stratification is still controversial and it is not yet recommended for local staging

in low-risk and intermediate-risk localized prostate cancer without predominantly Gleason pattern 4 [1].

We report on a population where transperineal biopsy using MRI-TRUS elastic registration was implemented to re-assess cancer grade and volume after TRUS-B reported low and intermediate-risk prostate cancer in contradiction to MRI findings.

Materials and methods

Prostate Cancer multidisciplinary meeting (PCMDM) was set as a weekly referral-based meeting to collegially review all cases of localized prostate cancer. Transperineal Elastic-Registration image-guided biopsies (TPER-B) of the index target (IT) defined as the largest lesion with Prostate Imaging-Reporting Data System-v2 (PIRADS) ≥ 3 were organized when the results of prior TRUS-B in terms of cancer position, core length or Gleason grading were discordant with MRI findings. Of note, no central review of TRUS-B biopsy was organized.

MRI sequences, obtained without endorectal coil, followed the European consensus meeting [7] and were reported according to the PIRADS guidelines [8]. IT was characterized in diameter and location [7] (Fig. 1a).

Biopsy procedure

Two operators (DP, BM) performed the biopsies. TPER-B of the IT used a CE-Marked, FDA-approved MRI/3D-TRUS transperineal image-guided system (TRINITY(R) workstation, Koelis, Grenoble, F). MRI axial sections were
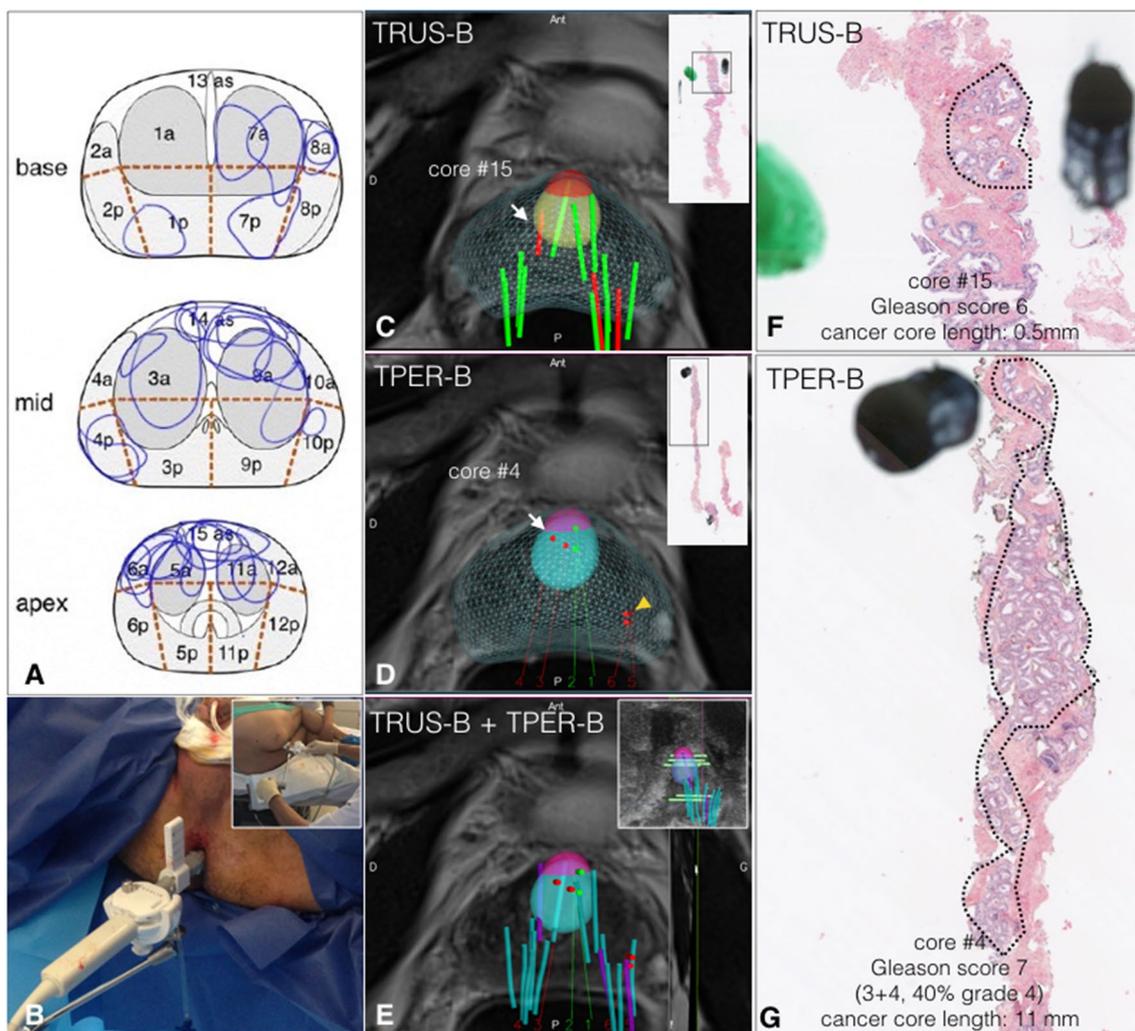
Fig. 1 **a** Location of the index targets according to the 27-sector diagram. **b** TPER-B under general and local (inset) anesthesia; **c** and **f** Case#4, 3D positioning of TRUS-B cores, small volume Gleason 6 cancer; **d** and **g** TPER-B demonstrating 11 mm long Gleason 7 (3+4) cancer. **e** relative positioning of TRUS-B and TPER-B cores in relation to 14 as 15 mm large index tumor

contoured to obtain the reference MRI prostate volume and to model the IT as the smallest sphere that encompassed the largest axial dimension of the target. The reference TRUS prostate volume was obtained by means of a side-fired motorized transrectal probe held in position by articulated probe holder (STEADYPRO(R), Fig. 1b). The workstation produced elastic registration of MRI and TRUS reference volumes, which allowed the target to be displayed within either TRUS or MRI reference volumes in the axial and sagittal planes. After rotating the probe to position the IT within the sagittal plane, a reusable needle guide (PERINEGRID(R)) with holes spaced 3 mm apart was attached to the probe in the sagittal plane. Virtual cores were reported in the MRI and TRUS reference volumes, as lines on the sagittal section and dots onto the axial sections, thereby allowing selecting the hole best suited to biopsy a particular region of interest. For each core, the position of the needle within the prostate volume was registered using proprietary Organ-based TRACKING(R) technology by repeating TRUS acquisitions with the needle in situ. The position was archived by the workstation as a 23-mm-long line segment that could be manually adjusted in depth, if needed. Complementary cores were obtained at the discretion of the operator from secondary targets or in a random-systematic pattern. The procedure was organized according to operator and patient's preferences under general anesthesia in the supine position or under perineal local anesthesia in the left lateral position. At the end of the procedure, the cores were numbered and referenced to MRI and 3D-TRUS archives (Fig. 1c–e).

Multidimensional risk-stratification

All TPER-B biopsy were analyzed by a single senior uro-pathologist (MLQR) with > 10 years of experience. Cores were individually processed to document on the presence and length of cancer (Fig. 1f, g). Grading was performed according to the World Health Organization classification [9] and ISUP consensus conference [10]. Results were dichotomized for comparison according to the presence of grade 4 glands (Gleason score-6/ISUP grade group 1 vs. Gleason score-7 (3 + 4) and (4 + 3), ISUP Grade groups 2 and 3). Surrogates of cancer volume were reported as the longest stretch of cancer on any positive core (maximum cancer core length: MCCL) and the cumulated length of cancer made available for pathology (total cancer core length: TCCL) [11]. Risk groups were stratified according to the University College London (UCL) definitions for clinical significance on transperineal biopsies [12] (definition 1: Gleason score ≥ 4+3 and/or MCL ≥ 6 mm,

definition 2: Gleason score ≥ 3+4 and/or MCL ≥ 4 mm) and the EAU risk groups for biochemical recurrence [1].

Statistics

For descriptive analyses, medians and interquartile ranges (IQR) or 95% confidence intervals (95% CI) are presented for continuous variables, whereas absolute values and percentages are provided regarding categorical variables. Welch's unequal variance t test compared quantitative variables with qualitative outcomes. Yate's corrected Chi-square test evaluated the association between categorical variables. All p values were two sided. Statistical significance was set at $p < 0.05$ (Prism v5.0, GraphPad Software, Inc. SanDiego, CA, USA).

Results

Of the 237 prostate cancer patients reviewed from January to April 2018, 30 were offered repeat transperineal biopsies for risk-stratification [Median and (IQR) values; age: 67 years (62–74), PSA: 8.8 ng/mL (5.9–12.1)], after one (14/30, 46.7%), two (8/30, 26.7%) or three (8/30, 26.7%) sets of transrectal biopsies. Digital rectal evaluation (DRE) was unsuspicious (T1c) in all but 6 patients (cT2a: 20.0%). 18/30 (30.0%) showed low-risk and 12/30 (40.0%) intermediate-risk localized prostate cancer [1] (Fig. 2). Sixteen (16/30, 53.3%) were engaged into active surveillance while treatment decision was still pending in 14 (14/30, 46.7%).

Median prostate volume was 42 mL (IQR: 30–62), median IT diameter was 12 mm (IQR: 8.5–17.5). IT's are positioned in Fig. 1a.

Median time interval between TRUS-B and TPER-B was 5.5 months (IQR: 3.2–9.1) with a median number of cores taken at the last set of TRUS-B of 14 (IQR: 12–16) in a random systematic manner in 9/30 (30.0%) patients, a cognitive manner in 9/30 (30.0%) or using a software-assisted elastic registration technique in 12/30 (40.0%) patients.

After verbal informed consent, eight transperineal cores on average [Median and IQR: 8 (6–9)] were taken, of which six in the IT (IQR: 4–6). The procedure was successfully completed under general (17/30 patients, 56.7%) or local (13/30, 43.3%) anesthesia. More cores were taken under general anesthesia [Median and IQR: 8 (7–11) vs. 6 (6–8), respectively, $p = 0.03$], although no differences were observed regarding the number of cores addressing the IT [7 (6–8.0) vs. 5 (4–6), n.s., $p = 0.48$] nor overall cancer detection (14/17 vs. 9/13 not significant. $p = 0.66$).

Compared to prior TRUS-B of the whole gland, TPER-B of the IT obtained longer tumor samples for analysis both in terms of MCCL [Mean and (95% CI): 2.6 mm (1.9–3.3) vs. 6.9 (5.0–8.8), respectively, $p < 0.0001$]
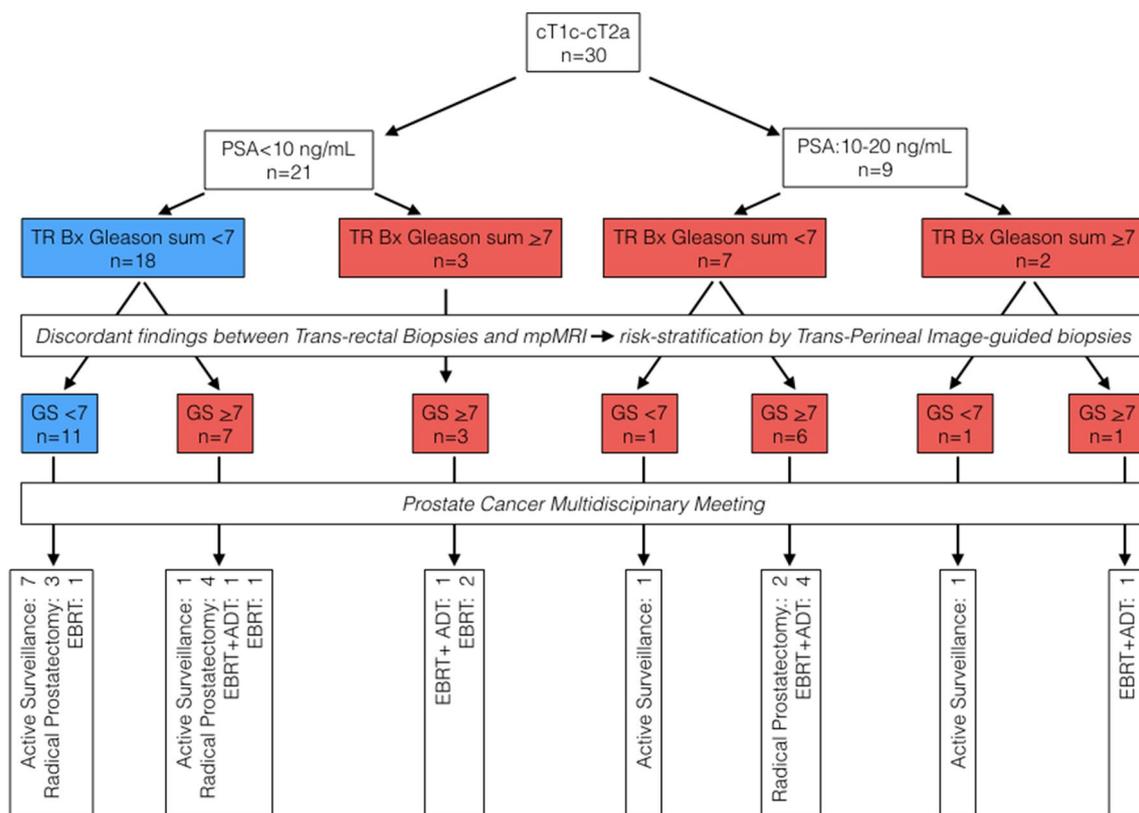
Fig. 2 Characteristics of 30 patients before and after risk-stratification by transperineal image-guided elastic-registration biopsies. Blue box: Low risk, Red box: Intermediate risk, according to the EAU risk groups for biochemical recurrence. After transperineal biopsies, Gleason score < 7 denotes Gleason score 6 cancer or negative repeat biopsies

and of TCCL [3.6 mm (2.6–4.5) vs. 19.7 (11.6–27.8), $p = 0.0002$]. Intriguingly, longer MCCL [Mean and (95% CI): 8.7 mm (6.7–10.7) vs. 4.1 mm (0.6–7.6), $p = 0.002$], and TCCL [Mean and (95% CI): 32.3 mm (21.5–43.0) vs. 6.9 (0.5–14.8), $p = 0.0004$], were measured in Gleason score7/ ISUP grade groups 2 and 3 cancers on TPER-B while it was the contrary for TRUS-B [MCCL: 1.0 mm (0.5–1.8) vs. 2.9 mm (2.1–3.7), $p = 0.0007$; TCCL: 2.1 mm (0.5–4.3) vs. 3.9 mm (2.8–5.0), not significant ($p = 0.09$)]. The shift in grading resulting from the transperineal approach (Fig. 3) translated into upgrading 13/30 (43.3%) patients. Complementary biopsies that were taken in 16 patients (16/30, 53.3%) showed small foci of well-differentiated cancer in five patients and one focus of Gleason score 7a (3 + 4) in one patient (case#4, Fig. 1d, yellow arrowhead). They did not add to the information obtained from the IT. In seven patients (7/30, 23.3%), transperineal biopsies of the IT only showed active inflammation.

Regarding clinical significance, 14/30 (46.7%) patients met UCL-definition 1 and 18/30 (60.0%) of UCL-definition 2 (Fig. 3). 7/16 (43.8%) patients under active surveillance simultaneously met the two definitions and were re-allocated toward prostatectomy ($n = 4$) or radiation therapy ($n = 3$).

In patients not yet assigned, TPER-B risk-stratification supported the predominant selection of treatments with curative intent (prostatectomy:5, radiation therapy:8, active surveillance:1). Figure 2 reports PCMDM decisions according to the EAU risk-groups [1].

Discussion

The most important driver of repeat biopsies was a discrepancy between MRI and Gleason score from TRUS-B, notably low apparent diffusion coefficients on diffusion-weighted imaging, which in recent meta-analysis showed adequate sensitivity and specificity in the detection of high-risk cancer [13]. It proved effective as most Gleason score-6 patients (13/25, 52%) were upgraded to Gleason score-7 and re-allocated to treatments with curative intent. However, in seven patients (7/30, 23.3%), biopsies did not show cancer but active inflammation (Fig. 3). The issue of an incidental finding of inflammation was recently addressed in a cohort of 137 patients receiving in-bore biopsies for PIRADS 3–5 targets [14] where the same proportion (27%) of lesions also showed inflammation but no cancer, mainly in equivocal
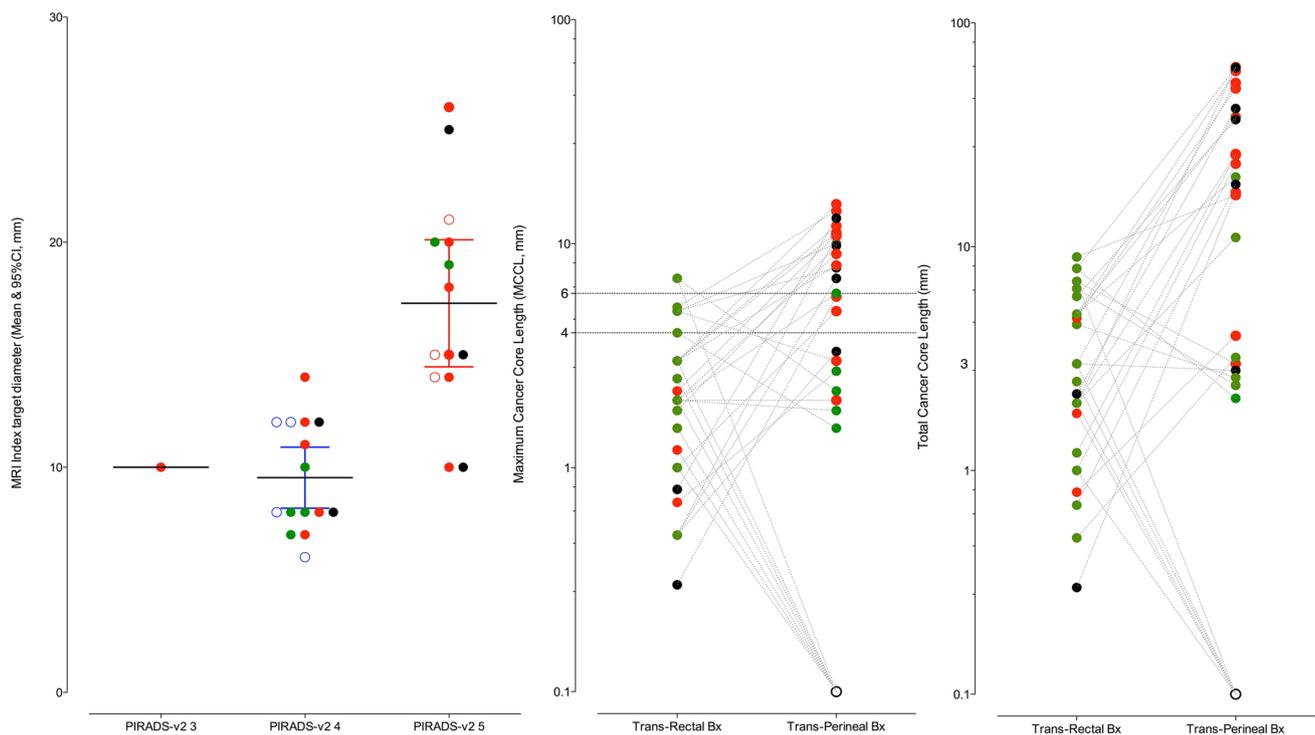
Fig. 3 a Index target PIRADS characteristics in relation to transperineal biopsies (TPER-B) results. Matched-pair representation of Maximum Core Cancer Length (**b**: MCCL) and Total Core Cancer Length (**c**: TCCL) on transrectal biopsy (TRUS-B) and TPER-B. For MCCL, 4 and 6 mm thresholds derived from University College Lon- don definitions of clinically significant cancer are indicated. Gleason grade and ISUP Grade group are color- coded. Green: Gleason grade 6 (3+3), ISUP grade group 1, Red: Gleason grade 7 (3+4), ISUP grade group 2, Black: Gleason grade 7 (4+3), ISUP grade group 3. Empty circles illustrate the absence of cancer

PIRADS 3–4 targets (58 and 39%, respectively) but only rarely in PIRADS 5 targets (3%). It is not known whether the high proportion of negative PIRADS 5 lesions (3/14, 21.4%) we observed reflected recent history of TRUS-B, imperfect evaluation of a clinically significant target or was circumstantial in a small cohort. Patients were nevertheless offered close active surveillance with 6-month MRI follow-up.

The second driver was discordance in position of the positive TRUS-B cores and the IT. Since standard random systematic TRUS-B is taken as far posterior and lateral possible from the peripheral gland [1], it was hypothesized that targets located anteriorly in the prostate (Fig. 2) were likely under-evaluated. In most patients, however, MRI informed TRUS-B. We reported that millimeter precision was crucial for cancer detection and that cognitive biopsies lacked precision compared to those obtained with deformable MRI-TRUS image registration [15]. Even with software assistance, accessing from the rectal wall those lesions anterior to the urethra is challenging. However, transperineal cores that run parallel to the longitudinal axis of the prostate are in geometrical terms better suited to address anterior targets, than TRUS-B that are constrained by their eluding intersecting the urethra (Fig. 2). They are also more likely to sample the largest dimensions of the tumors, which are often oval in

shape [16] and follow the planes of lowermost resistance of the zonal anatomy [17], with the theoretical benefit of bringing more cancer tissue for analysis. Indeed, transperineal biopsy proved to be well correlated with cancer extent and differentiation assessed on prostatectomy specimens [18].

Recent advances further spurred interest in the transperineal approach. First, while systematic mapping of the prostate volume entailed a large number of cores that required general or spinal anesthesia, it was demonstrated that cognitive targeting of MRI suspicions identified with fewer cores the same rate of clinically significant cancer than 20-sector transperineal mapping [19]. Second, the resulting reduction in core numbers allowed taking transperineal biopsies under local anesthesia with minimal patient's discomfort [20]. Third, the limitations of transperineal cognitive biopsies, where targeting is approximated from conventional anatomical landmarks and does not include procedural control of its precision, are now addressed by fusion technologies.

The rigid-registration BiopSee$^{(R)}$ system compared transperineal targeted biopsy to template saturation biopsy. Both showed comparable detection rates of Gleason score ≥7 cancer, although the authors ultimately advocated their combination for cancer detection [21]. However, rigid registration does not account for the movements and deformations of the

prostate gland incurred during biopsies [22], while elastic registration designed to control prostate motion [23] was shown to improve the precision and detection rates of clinically significant cancers [15].

To the best of our knowledge, the recent analysis represents the first matched-paired comparison of cancer differentiation assessed through the consecutive prisms of TRUS-B and TPER-B. On needle biopsy, the Gleason score is based on the predominant and the highest-grade patterns making the detection of any pattern of 4 or higher of particular importance [10]. However, tangentially sectioned well-formed separate glands (pattern 3) may impose for poorly formed irregular glands (pattern 4), a known limitation of Gleason grading in small specimens [24]. Compared to TRUS-B, we observed that TPER-B obtained longer MCCL and that a positive relationship existed between longer MCCL and Gleason score 7 ($3 + 4/4 + 3$). In that respect, TPER-B showed value in controlling the classical diagnostic pitfall of small specimens, thereby optimizing Gleason grading, a crucial determinant in treatment decision. Although no consensual definitions exist on the characteristics of image-guided biopsies that would signal clinically significant cancer [25], the UCL group showed that for transperineal cores MCCL and Gleason score correlated with clinically significant cancer foci, greater than 0.5 mL (UCL-definition 1) or 0.2 mL (UCL-definition 2) [12]. Here, a significant minority (43.8%) of patients under active surveillance met both definitions and were re-allocated after MDPCM to treatments with curative intent.

Limitations to this study are manifold. First, it is retrospective although based on data prospectively accrued. Second, it mostly used the prism of cancer differentiation to stratify risk but did not include central review of TRUS-B although Gleason grading shows significant variability among general [26] and urologic pathologists [26]. This may be mitigated by the integration in the decision process of the maximal cancer core length, such as pioneered in the UCL definitions of clinically significant cancer [12]. Alternately, as illustrated here by TRUS-B, short stretches of cancer tissue are prone to under-grading. They should be accepted only with caution after confrontation with MRI findings. Last, the most important was the preliminary nature of this short series. However, its results remained consistent with the known limitations of TRUS-B and the current understanding of the organization of cancer foci within the prostate volume.

Conclusion

When MRI analysis did not concur with the diagnosis obtained by TRUS biopsies of small volume low and intermediate-risk prostate cancer, image-guided transperineal

biopsies of the index target provided more cancer material for pathology. Subsequent re-evaluation of cancer volume and grade switched a majority of patients towards higher-risk groups and treatment with curative intent.

Author contributions BC: data collection, and manuscript review; MR: data collection, data analysis, and manuscript review. M-LQ-R: data collection, and manuscript review. PG: data analysis, and manuscript review. JK: manuscript review. RA: data collection, and manuscript review. GP: data analysis, and manuscript review. DP: Study development, data analysis, and manuscript review. BM: Study development, data collection, data analysis, manuscript writing.

Compliance with ethical standards

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