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TOPIC PAPER

Follow-up of negative MRI-targeted prostate biopsies: when are we missing cancer?

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Abstract

Introduction Multiparametric magnetic resonance imaging (mpMRI) has improved clinicians' ability to detect clinically significant prostate cancer (csPCa). Combining or fusing these images with the real-time imaging of transrectal ultrasound (TRUS) allows urologists to better sample lesions with a targeted biopsy (Tbx) leading to the detection of greater rates of csPCa and decreased rates of low-risk PCa. In this review, we evaluate the technical aspects of the mpMRI-guided Tbx procedure to identify possible sources of error and provide clinical context to a negative Tbx.

Methods A literature search was conducted of possible reasons for false-negative TBx. This includes discussion on false-positive mpMRI findings, termed "PCa mimics," that may incorrectly suggest high likelihood of csPCa as well as errors during Tbx resulting in inexact image fusion or biopsy needle placement.

Results Despite the strong negative predictive value associated with Tbx, concerns of missed disease often remain, especially with MR-visible lesions. This raises questions about what to do next after a negative Tbx result. Potential sources of error can arise from each step in the targeted biopsy process ranging from "PCa mimics" or technical errors during mpMRI acquisition to failure to properly register MRI and TRUS images on a fusion biopsy platform to technical or anatomic limits on needle placement accuracy.

Conclusions A better understanding of these potential pitfalls in the mpMRI-guided Tbx procedure will aid interpretation of a negative Tbx, identify areas for improving technical proficiency, and improve both physician understanding of negative Tbx and patient-management options.

Keywords Multiparametric MRI · Targeted prostate biopsy · Prostate cancer · Fusion prostate biopsy · PIRADS

Introduction

Multiparametric magnetic resonance imaging (mpMRI)-transrectal ultrasound (TRUS) fusion-targeted biopsy (Tbx) represents a substantial step forward in the detection of prostate cancer (PCa). When compared to the standard-of-care 12-core systematic biopsy (Sbx), Tbx detects greater rates of intermediate- and high-risk disease and lower rates of low-risk disease [1]. Given the incidence of prostate cancer in American men [2], Tbx may provide larger and more accurate specimens enabling the true grade of disease to be established with lower risk of subsequent upgrading. This helps determine which patients require intervention and those who may be managed with active surveillance. In their seminal paper on mpMRI and Tbx, Siddiqui et al. reported a sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of 77%, 75%, and 70%, respectively, for detection of clinically significant prostate cancer (csPCa) [1]. The PROMIS study reinforced these findings by showing how use of mpMRI with biopsy could rule out up to 89% of csPCa compared to only 74% by TRUS biopsy alone [3]. Furthermore, the PRECISION trial randomized biopsy-naive patients to either systematic biopsy alone or MRI with or without targeted biopsy if the MRI showed a suspicious

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lesion of the MRI with targeted biopsy group was able to detect 38% of csPCa compared to 26% in the TRUS biopsy group [4]. However, despite advances in imaging and Tbx, it is not uncommon that the Tbx of a suspicious lesion seen on MRI is not confirmed to be csPCa. Urologists are faced with the dilemma of a positive mpMRI but a negative Tbx. Here, we provide an approach to this situation.

Historically, prostate-specific antigen (PSA) levels have driven the decision to biopsy the prostate. In the era of mpMRI, standardized risk assessment tools, such as the Prostate Imaging Reporting and Data System version 2 (PIRADSv2), have improved predictions for csPCa defined as lesions with a Gleason Score > 6 or diameter > 0.5 cm. In a meta-analysis of 13 studies totaling over 2000 pooled patients who underwent prostate MRI scored via PIRADSv2 [5], the overall sensitivity was 85% for csPCa with a specificity of 71%. Accuracy improved with more sophisticated imaging equipment (3.0T MRI and endorectal coil) and with increased reader experience [5]. A study by Mehralivand et al. [6] examined PIRADSv2 performance by stratifying the results according to PIRADS scores. They found that PIRADS 5 lesions were confirmed to represent csPCa in 72.4% of such cases, while PIRADS 4 lesions only identified csPCa in 22.1%. This high false-positive cancer detection rate for PIRADS 4 lesions has similarly been observed in other studies of the PIRADSv2 scoring system [7, 8]. Therefore, there is significant uncertainty when a prostate lesion is scored on mpMRI as likely csPCa (e.g., PIRADS 4 or 5), but Tbx results are negative. These high rates of false positive mpMRI findings offer context to negative biopsies and perhaps bolster confidence in such results. Additionally, the meta-analysis [5] and separate multi-reader study by Rosenkrantz et al. [8] suggest there is still a large portion (10–15%) of csPCa undetected by mpMRI and Tbx.

Therefore, the interpretation of a negative MRI-guided Tbx result is highly specific for each clinical scenario. The NPV of Tbx is heavily influenced by the prostate tissue characteristics, image acquisition, and Tbx technique, and to add further complexity, these diagnostic tests are imperfect even in ideal circumstances. A literature review was performed with these factors in mind to evaluate the potential pitfalls of what may cause false negative imaging results as well as the predictive capability of a commonly used scoring system, challenges in obtaining high quality images, and potential difficulties with fusion registration and biopsy acquisition. In this review, we aim to offer insight into these challenging clinical scenarios by highlighting possible causes for both true- and false-negative Tbx and potential options for managing these cases.

Potential causes of negative MRI-TRUS fusion biopsies

Different MRI-guided Tbx techniques

PCa detection results vary among the different techniques for performing Tbx. The most studied method is software-based registration of mpMRI and TRUS called fusion Tbx. Additionally, cognitive fusion Tbx, in which operators mentally combine information from the mpMRI and TRUS to target lesions, or in-bore MR-guided Tbx, in which biopsy and MRI acquisition occur with the patient in the MR scanner, have each been studied [9, 10]. Comparative studies suggest MR-guided approaches are more accurate for PCa detection, but more method-specific distinctions among these approaches have yet to be made [9, 11]. Kaufmann et al. looked at the rate of detection of csPCa of patients receiving in-bore MR-guided biopsies and detected csPCa in 40% of patients compared to 23.7% with cognitive fusion, however, due to a small sample size, this was not statistically significant [9]. Additionally, cognitive fusion biopsies are highly dependent on the user with some studies showing inferiority to fusion Tbx [9]. However, the PROFUS trial showed that at a center with considerable experience, fusion Tbx and cognitive fusion did not yield significantly different csPCa detection rates, 20.3% vs. 15.1%, respectively, with cases of smaller lesions likely benefiting the most from fusion software [12]. Therefore, when evaluating a negative Tbx result, one must consider the entire chain of events beginning with the MRI and ending with the biopsy.

False-positive mpMRI

Selection of lesions for Tbx relies on PIRADSv2 score to determine the likelihood of csPCa. As previously described, even PIRADS 5 lesions can misrepresent a prostate lesion. Potential causes of false-positive MRI findings include focal hyperplasia, inflammation, fibrosis, and pre-malignant conditions such as high-grade intraepithelial neoplasia [13]. These benign findings often have MR characteristics that overlap with imaging features of PCa (Fig. 1).

Benign prostatic hyperplasia (BPH) nodules, when comprised of stromal tissue, display low T2 signal intensity with restricted diffusion and early contrast enhancement, the same features found in PCa transition or central zone lesions. The sharply defined borders and symmetry of BPH nodules help distinguish them from PCa [14]. Prostatitis, both bacterial and granulomatous, is another common benign condition confused with PCa on mpMRI

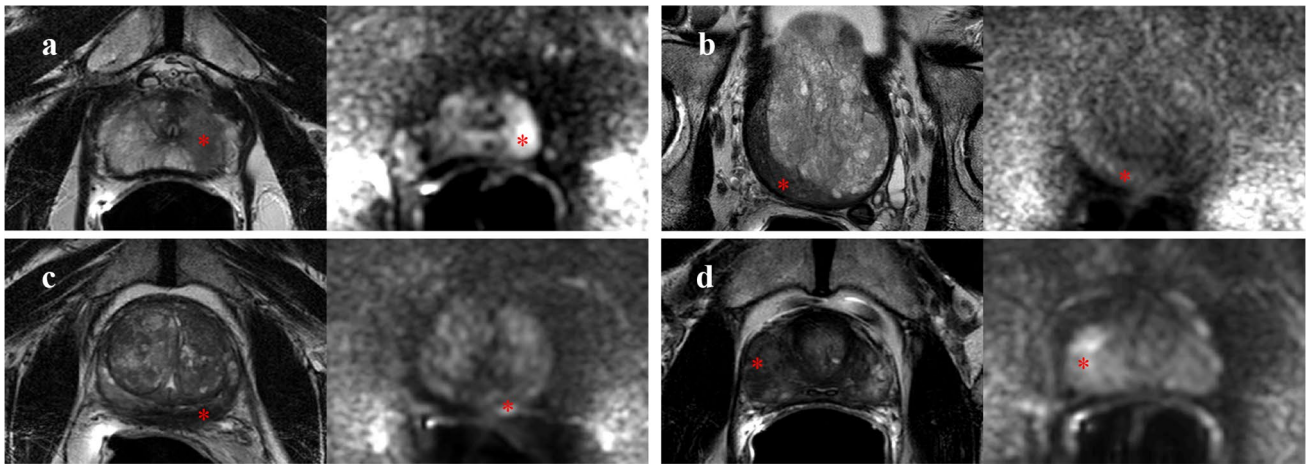

Fig. 1 True- and false-positive mpMRI PIRADS 5 lesions; axial T2 W (right) and b2000 DWI (left): **a** prostate adenocarcinoma, **b** high-grade prostatic intraepithelial neoplasia (HGPIN), **c** chronic inflammation with diffuse histiocytes, and **d** necrotizing granulomatosis after BCG therapy

[13]. On a cellular level, the increased cellular density due to inflammation or hyperplasia results in low T2 signal, moderately restricted diffusion, and increased and early contrast enhancement [15, 16]. Not uncommonly, normal appearance of fibromuscular stroma, which is characterized by low T2 signal and decreased ADC values, may be mistaken for an anterior prostate tumor [13, 14, 17]. Following a prostate biopsy, hemorrhage can mimic and/or obscure the appearance of a PCa lesion on mpMRI by appearing markedly hypointense on T2 W and hyperintense on DWI [14, 18]. Comparison with T1 W imaging will aid in hemorrhage identification [14].

Other less common scenarios that may result in mpMRI falsely positive for PCa including cystic prostate disease, prior brachytherapy, androgen deprivation, etc. Experience reading prostate mpMRI and detailed clinical history taking can help identify these false positives and help validate a negative Tbx. Moreover, early research suggests that discrepancies in PIRADS scores between dominant and non-dominant mpMRI sequences may suggest false-positive lesions [19].

Numerous technical factors during the mpMRI can also impede successful interpretation of the prostate image. For instance, motion artifact, presence of prosthetic such as a hip replacement, poor choice of MR parameters, insufficient signal-to-noise ratio, or susceptibility artifacts from bowel gas can all challenge csPCa detection. Previously published MRI parameters are available for best practice guidance in overcoming these potential technical pitfalls [20].

False-negative Tbx

As an emerging technology, Tbx is not immune to inherent flaws. In these circumstances, mpMRI correctly identifies a malignant lesion, but Tbx results are falsely negative due to a system or user error.

Following mpMRI identification of a suspicious lesion, targets for biopsy are marked, and the MR image is fused to the real-time TRUS image [1, 21]. This allows the spatial resolution and lesion characterization of MRI to be combined with real-time TRUS images to enable sampling of MRI targets in real-time. Commercially available platforms include software that registers the MR image with the TRUS image and while the platforms are different in their approach to this, the principle is the same. Precise acquisition of tissue depends on successful image registration and fusion. If the images are not correctly registered, a biopsy that appears on the software platform may be off-target if the two images are misregistered. Even when studied in an experimental setting, fusion systems tend to report a registration error between 1 and 3 mm [22–24]. Therefore, careful attention must be given to segmentation of the prostate edges at the beginning of the procedure. If the user notes that the anatomy is not properly aligned, a rotational and translational correction can be applied to better align the two images interprocedurally. Regions of interest located anteriorly or towards the prostatic base are particularly susceptible to registration error. Axial MRI slices and axial TRUS imaging have slightly different planes of exploration; the discrepancy is magnified further from the TRUS probe [25]. Bladder or prostate capsule edges can by utilized as anatomical landmarks to guide registration during correction or users can practice with simulation tools if desired [25, 26].

Prostate deformation during MRI or TRUS can lead to difficulties in accurately registering images. There are many causes of prostate gland deformations during the procedure that are not represented by the initial mpMRI. These changes in prostate and/or lesion size increase the

risk of registration error. Causes include alteration of rectal position due to placement of endorectal coil during MRI or TRUS probe during biopsy, as well as changes in patient position, or degree of bladder filling between imaging sessions [21, 27]. One must also consider that biopsy may often take place months after the MRI and cannot account for any glandular changes that occur in the interim. Fusion platforms attempt to overcome discrepancies by spatially orienting the prostate targets relative to surrounding organs, use of elastic registration algorithms, tracking via electromagnetic field, or using an articulating arm attached to the TRUS probe [22–24, 27].

When registration is successful, there is still opportunity for error during the biopsy itself. There is a learning curve in performing Tbx. Calio et al. showed that as experience with Tbx increased, csPCa detection rates increased and rates of Gleason Score upgrading at time of prostatectomy decreased [28]. Furthermore, lesion size and its orientation within the prostate may make Tbx more difficult. As the needle penetrates rectal and prostatic tissue, it can deflect off course [29]. In a study by Halstuch et al., needle deflection was measured as approximately 2 mm and worsened in larger prostates and right-sided lesions [30]. When targeting small lesions measuring only millimeters in their largest dimension, even slight needle deflections can result in missed biopsy. Physicians should confirm on real-time US that the biopsy needle is reaching the intended target after needle deployment (Fig. 2).

Recommendations for improved Tbx accuracy

As a new technology, Tbx will continue to benefit from incremental engineering improvements. Currently, there is no standard guideline for Tbx sampling of a lesion, which can range from a single biopsy core to a saturation biopsy. Previous studies have determined systematic saturation biopsies improve cancer detection versus 12-core systematic biopsies especially at low PSA values albeit with considerable morbidity [31, 32]. Presumably, Tbx cancer detection would improve with additional cores obtained, but an optimal number of cores per lesion have yet to be established. With a learning curve for Tbx adoption, obtaining additional cores early on may improve accuracy until technique improves [28]. The benefit of obtaining additional biopsy cores must be weighed against potential harm to patients, such as discomfort, hematuria, rectal bleeding, and sepsis.

Management of a negative Tbx

Since there are a variety of causes for false-negative Tbx, patient management in these circumstances depends on identifying any sources of error to rule out missed disease

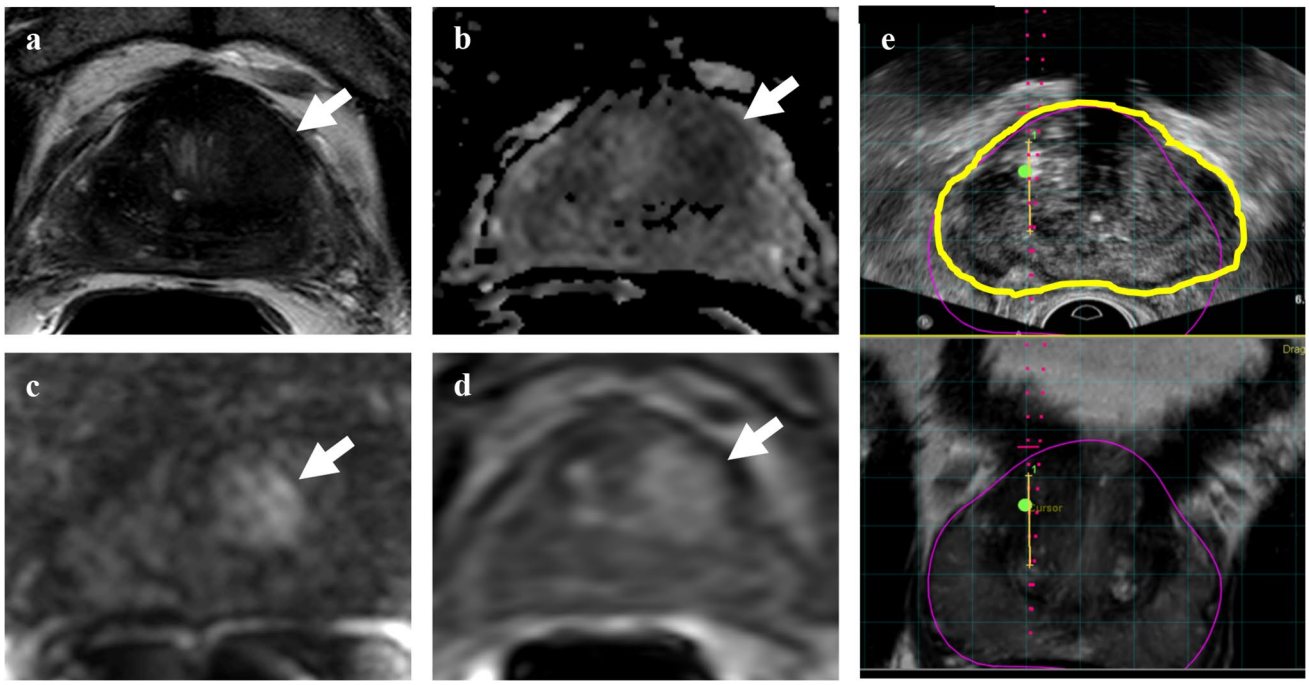

Fig. 2 Missed targeted biopsy: 54-year-old man with a serum PSA = 15.44 ng/ml. Axial T2 W MRI shows a PIRADS 5 lesion in the left base anterior transition zone (arrow) (**a**), which shows restricted diffusion on ADC map (**b**) and b2000 DW MRI (**c**) (arrows) with increased vascularity on DCE MRI (**d**) (arrow). The lesion underwent TRUS/MRI fusion-guided biopsy and the result was cancer negative which is related to failure of TRUS (outlined in yellow) and MRI (outlined in pink) registration (**e**)

Table 1 Identification of potential sources of falsely negative targeted biopsies

	Source of error	Challenge for Tbx	Possible solution(s)
Imaging	PIRADSv2 scoring	High rate of false-positive lesions for PIRADS 4	Consider PCa mimics, evaluate clinical suspicion to rule out missed disease; detection improves with experience and equipment (e.g., endorectal coil)
	PCa mimics	Benign features share mpMRI characteristics with PCa	Work with GU radiologist to identify specific discrepancies between PCa and mimics
	Prostate hemorrhage	Hemorrhage from biopsy obscures mpMRI and possible lesions	Wait 2–3 months after injury/biopsy before re-imaging patient
Targeted biopsy	Registration error	Fusion software (or cognitive fusion) incorrectly merges mpMRI and TRUS images	Evaluate TRUS and mpMRI images to confirm registration based on local anatomic landmarks
	Needle deflection	Biopsy needle track altered during course to target	Review needle track 3D reconstruction, consider needle gauge to reduce deflection
	Experience level	Tbx accuracy limited by technical proficiency	Learning curve should be appreciated for new adoption of Tbx

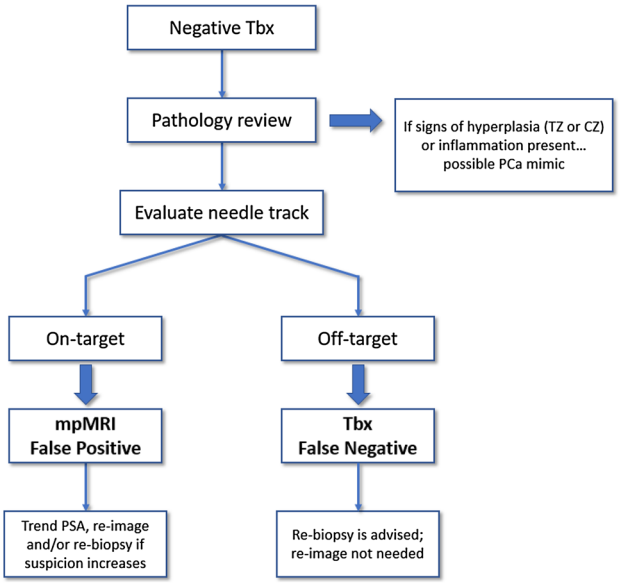

Fig. 3 Decision guide for management of negative Tbx

(Table 1; Fig. 3). Working backward, pathology should be reviewed to determine if a possible PCa mimic on mpMRI was sampled. This may include evidence of hyperplasia or inflammation in the biopsy sample. One must also confirm the accuracy of the Tbx. Fusion biopsy software can create three-dimensional images of the needle path relative to the suspicious lesion target to confirm accuracy of the biopsy. The quality of the registration can be retrospectively evaluated. If quality of registration is adequate and the needle is determined to have sampled the correct location, then attention should be directed back to the mpMRI and the clinical picture as this may be an example of a falsely positive mpMRI lesion. If the patient is of low clinical suspicion for csPCa or there is evidence of PCa mimics (e.g., prostatitis, BPH nodules, etc.), these patients can likely be managed with continued PSA monitoring and repeat mpMRI and/or biopsy based on clinical suspicion. Alternatively, if reconstruction of the needle path reveals missed biopsy or fusion registration error, then repeat biopsy should be considered.

In some cases, there may be neither a technical error during fusion biopsy nor concerns about the interpretation of the mpMRI. In these instances, physicians must re-evaluate the probability of the Tbx being falsely negative based on the patient's risk of harboring disease. Multiple studies have determined that factors such as PSA or PSA density, and increased age are risk factors for csPCa and existing nomograms are available to determine individual risk [33, 34]. High suspicion or a PIRADS 5 lesion with its high specificity for csPCa should be considered cancer until proven otherwise and these patients should have a repeat biopsy performed within a shorter time period. Those with a lower risk of disease may be monitored clinically with serial PSA values, DRE, and imaging when necessary with the caveat that post-biopsy hemorrhage may cause mpMRI misinterpretation up to 2–3 months after biopsy [18].

Lastly, it is important not to underestimate the role of the urologist–patient relationship in clinical management of these cases. Factors such as comorbidities, family history (e.g., prostate and breast cancer), race, genitourinary history (e.g., prostatitis, sexually transmitted infection), and life expectancy should be considered when evaluating PCa suspicion, and therefore, the need to re-biopsy patients. Urologists are positioned to consider the entire patient history when planning follow-up of a negative Tbx.

Conclusion

The challenge of a negative Tbx highlights the importance of close collaboration between urologists, genitourinary radiologists, and pathologists. As explained above, precise

understanding of detail in these cases can greatly influence the interpretation of a negative Tbx. Experience in prostate mpMRI acquisition and interpretation, prostate biopsy technique, and pathologic discrimination is imperative to discerning and remedying causes of falsely negative Tbx.

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