



## Review Article

## Shifting to transperineal prostate biopsy: A narrative review

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## ABSTRACT

**Objective:** To address the limitations and challenges associated with transrectal (TR) biopsy and to present transperineal (TP) biopsy as a viable and potentially safer alternative to TR biopsy. Prostate cancer (PCa) is a significant global health concern. The prevalence of advanced-stage prostate cancer in Asia is higher than that in the United States, emphasizing the need for effective screening and diagnosis methods. The gold standard of diagnosis is a TR biopsy. However, it has limitations due to the risk of infection and potential complications, such as injury to the rectal artery. Efforts have been made to address issues such as false-negative biopsies, under-sampling, and over-sampling through MRI-guided biopsies. However, the TR approach makes it difficult to access the apical and anterior regions of the prostate. TP biopsy has emerged as an alternative to address the limitations of TR biopsy. Nevertheless, a TP biopsy is a painful procedure, requiring the use of general anesthesia and expensive equipment. As a result, it has been perceived as costly and time-consuming. In addition, it requires a steep learning curve. The introduction of local anesthesia such as pudendal nerve block and the adoption of freehand techniques have contributed to the feasibility of performing TP biopsy. Recent research indicates that freehand TP biopsy can yield comparable diagnostic results to template-guided approaches. The diagnostic performance, cancer detection rates, and complication rates of TP biopsy have demonstrated its potential as a safe and effective diagnostic method.

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## 1. Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, with 1,414,259 reported cases. It ranks sixth on the list of leading causes of cancer-related deaths, with 375,304 fatalities, according to Global Cancer Observatory (GLOBOCAN) 2020 data.<sup>1</sup> PCa is the third most common form of cancer in 20 countries in Asia. The increase in the incidence of prostate cancer can be attributed to longer life expectancy and the adoption of a western lifestyle.<sup>2,3</sup> The prevalence of advanced-stage PCa in Asia except Japan is higher than that in the United States of America.<sup>4</sup> Metastases were present in 31% of patients in China at the time of diagnosis in one study.<sup>4</sup> Japan extensively employs prostate-specific antigen (PSA) screening, which is associated with a decrease in the proportion of advanced-stage PCa cases at the time of diagnosis.<sup>5,6</sup>

As a result, the importance of PCa screening and diagnosis in Asia is on the rise. PSA, digital rectal examination, and imaging are the main methods used in PCa screening.<sup>7</sup>

Imaging modalities include computed tomography (CT), transrectal ultrasound (TRUS), and magnetic resonance imaging (MRI). CT is mainly used in staging rather than in screening.<sup>8</sup> The presence of hypoechoic lesions might be an indication of suspicious findings when evaluating the prostate by TRUS.<sup>9</sup> However, 30% to 40% of PCa appear to be isoechoic.<sup>10</sup> Although recent advances in elastography, contrast-enhanced ultrasound, and micro-ultrasound have improved the ability to diagnose prostate cancer, TRUS is still insufficient to be used alone.<sup>11</sup> Multiparametric MRI is increasingly being used in the diagnosis of prostate cancer. MRI-targeted biopsies can be performed in cases where previous biopsies have been negative.<sup>12,13</sup> Multiparametric MRI uses high-resolution T2-weighted images, diffusion-weighted imaging, MR spectroscopic imaging, and dynamic contrast-enhanced MRI to increase the sensitivity of cancer detection.<sup>14</sup> Prostate MRI data and results are reported through a Prostate Imaging-Reporting and Data System (PI-RADS) (current version: 2.1).<sup>15</sup> PI-RADS 3 is indeterminate, while PI-RADS 4 and 5 are considered to be probably malignant. PI-RADS 4 has a positive predictive value of

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40%, and PI-RADS 5 has a positive predictive value of 69% for clinically significant prostate cancer (csPCa).<sup>16</sup>

If there is a suspicion of PCa after screening, a prostate biopsy should be performed. A prostate biopsy can be performed through a rectal or perineal approach. In the past, prostate biopsies have been performed from a perineal approach because of concerns about infection from the rectal approach.<sup>17</sup> After the introduction of systematic biopsy by Hodge et al and the development of TRUS, transrectal (TR) biopsy has become the gold standard.<sup>18</sup> Due to increases in the number of infections and resistant strains, there is now a paradigm shift toward transperineal (TP) biopsy.<sup>19,20</sup>

## 2. Transrectal biopsy

In the early days of prostate biopsy, TR biopsy was not preferred because of concerns about getting infected by fecal contamination.<sup>21</sup> After the introduction of TRUS, targeted biopsies have been attempted using TRUS. However, 30–40% of prostate cancers were difficult to distinguish from normal prostate parenchyma. Proliferative nodules in the transition zone also caused confusion, making a biopsy difficult.<sup>10</sup> The modern era of TR biopsy began with the introduction of systematic biopsy by Hodge et al.<sup>18</sup>

The systematic TR biopsy was initially performed by dividing the prostate into six zones. It has a detection rate superior to conventional targeted TR biopsy.<sup>18</sup> Disadvantages of systematic biopsy include false negative biopsies, undersampling, and over sampling.<sup>22–24</sup> Since there is a 70% chance that the tumor is located in the peripheral zone, it is necessary to perform a peripheral zone biopsy in addition to a conventional 6-core biopsy.<sup>25</sup> In view of side effects and cost, the current practice of 10 to 14 systematic biopsies has become well established. The sensitivity of TR biopsy for overall PCa is approximately 63%.<sup>26</sup> If there is a clinical suspicion of cancer with a biopsy-negative result, a saturation biopsy may be performed to increase the size of the biopsy core.<sup>27</sup>

With advances in MRI, the discussion has turned back to targeted biopsy. A meta-analysis by Schoots et al has found no difference between MR and systematic biopsy in overall PCa detection, although better outcomes were achieved for csPCa detection with MR.<sup>28</sup> Similar results have been found in a recent meta-analysis performed by Kasivisvanathan et al.<sup>29</sup> The American Urological Association guidelines state that an MR-targeted biopsy can be performed when prostate cancer is suspected with negative results from previous biopsies.<sup>13</sup>

There are three modalities for targeted biopsy using MRI: cognitive biopsy, MR fusion biopsy, and direct MRI-guided biopsy (in-gantry biopsy or in-bore biopsy). In a cognitive biopsy, the surgeon identifies the lesion on the MRI image and performs the biopsy while identifying landmarks on the TRUS. Several studies have shown that cognitive biopsy has a cancer detection rate of less than 50%.<sup>30,31</sup> An MR fusion biopsy refers to a biopsy using fused images of an MRI and a volumetric ultrasonogram. It shows a superior diagnosis in csPCa than systemic biopsy, although it shows no difference in the overall detection rate of PCa with systemic biopsy.<sup>32</sup> Direct MRI-guided biopsy, also known as in-gantry or in-bore biopsy, involves the placement of the patient in an MRI gantry (bore) with simultaneous identification and biopsy of a suspicious lesion identified on a previous MRI. This has been shown to have a higher detection rate for csPCa with a lower number of biopsy cores than systemic biopsy.<sup>33</sup>

TR biopsy has a number of disadvantages due to its access through the rectum. First, it is difficult to gain access to the apical and anterior regions of the prostate.<sup>34</sup> Secondly, although prophylactic administration of antibiotics prior to the procedure is recommended, infection and sepsis can still occur.<sup>35</sup> Hospital admissions following a biopsy are increasing due to the rise of multi-

resistant bacterial organisms.<sup>36,37</sup> Third, if the rectal artery is injured, additional procedures such as clipping and cautery might be required. TR biopsy has traditionally been considered the gold standard because it can be easily performed in the office following local anesthesia and prophylactic antibiotics. However, the increasing incidence of major complications has led to increased research into TP biopsy.

## 3. Transperineal biopsy

Prior to the development of TRUS, TP biopsy was performed using a variety of techniques, including needle punch biopsy, open biopsy, aspiration biopsy, digit guide biopsy, and others.<sup>17,38</sup> Originally, TP biopsy was considered a better approach than TR biopsy due to concerns about infection in the rectal area. However, after the development of TRUS and the introduction of systematic biopsy, TR biopsy is identified as the gold standard because it is more efficient and convenient than TP biopsy, whereas TP biopsy has not advanced for a while. With the rise in infection rates despite prophylaxis and the escalation of antibiotic selection, concerns about TR biopsy have increased. Thus, TP biopsy is beginning to receive renewed attention.<sup>35–37,39</sup>

In order to improve the detection rate of TP biopsy, it is necessary to increase the number of biopsy cores.<sup>40,41</sup> This can be accompanied by an increase in perineal puncture, which can cause patient pain. This has led to the use of general anesthesia for TP biopsy, which has resulted in the occupation of inpatient wards or operating rooms in hospitals with an increase in costs.<sup>42</sup> The use of a brachytherapy grid during a TP biopsy has been gaining attention due to the need for precise access in the development of focal ablation.<sup>41,43</sup> With the development of local anesthesia methods and assessment techniques, it has become possible to perform a TP biopsy in an office setting.

### 3.1. Local anesthesia

A TP biopsy is more painful than a TR biopsy because it passes through the pelvic floor and bulbocavernosus. Therefore, appropriate anesthesia is necessary to reduce a patient's pain. There are several types of nerve blocks, including pudendal nerve block, periapical triangular block, and branch of pudendal nerve block.<sup>44</sup> For pudendal nerve block, anesthesia is administered just below the ischial spine, past the lesser sciatic foramen.<sup>45,46</sup> Branch of pudendal nerve block involves inserting an anesthesia needle 1.5 cm above the upper anal border and 2 cm lateral to the midline, followed by injecting lidocaine between the prostate capsule and superficial fascia under TRUS guidance, targeting the pudendal nerve branch in this area.<sup>47</sup> Periapical triangle block is a block anesthesia performed in the space between the levator ani muscle, the rhabdosphincter muscle, and the external anal sphincter muscle, called the periapical triangle.<sup>48</sup> A pudendal block is difficult to learn and technically demanding. Even with Doppler ultrasound, there is a possibility of surrounding tissue injury. A periapical triangle block has not been well studied.<sup>47</sup> A recent multicenter study has shown that perineal nerve blocks are more effective than the commonly used periprostatic block for TR biopsy.<sup>49</sup> Complications of pudendal block include nerve damage, bladder or rectal injury, and intravascular injection after pudendal artery puncture, which can be fatal.<sup>46</sup>

### 3.2. Assessment techniques: freehand biopsy

For assessment techniques, the development of freehand techniques is noteworthy. Freehand techniques can be divided into three main types: the fan technique, the probe-mounted grid, and

the probe-mounted cannula. The fan technique is not well defined yet. It is being referred to as double-freehand, true-freehand, or freehand without a needle guide.<sup>50,51</sup> The procedure involves selecting one puncture site in each of the two lobes of the prostate and inserting a coaxial biopsy needle at various angles, similar to a fan, to obtain prostate tissue.<sup>52</sup> Once the puncture site is identified, a coaxial cannula is first positioned at the intended perforation site in some cases (e.g. CamProbe).<sup>53</sup> The fan technique requires only TRUS and a coaxial needle for preparation. However, it has a very steep learning curve.<sup>54</sup> The probe-mounted grid is similar to the traditional brachytherapy grid and stepper method (e.g. SureFire-delta surgical, Trinity Perine-KOELIS, and UA1232 puncture attachment-BK Medical). It may require multiple punctures.<sup>53</sup> The probe-mounted cannula technique utilizes an access cannula to maintain alignment between the biopsy needle and the TRUS probe (e.g. EZU-PA3U-FUJIFILM and PrecisionPoint-BXTAccelyon).<sup>55,56</sup> This freehand method utilizes the mobility of the perineal skin and ischiorectal fat, allowing for freedom of movement and access to all parts of the prostate.<sup>57</sup>

### 3.3. Robot assisted transperineal biopsy

Robot-assisted TP biopsy has also been on trial. The site to be biopsied is first mapped by MRI. The robot is then positioned. Initially, a common access cannula is inserted. The robot then guides to preplanned areas for tissue examination, allowing the operator to perform a prostate tissue biopsy. A study by Ho et al showed that there was no sepsis or bleeding after biopsy.<sup>58</sup> Yang et al have performed a robot-assisted TP biopsy under local anesthesia and found no conversion to general anesthesia.<sup>59</sup> A study by Miah et al showed a detection rate of 51.2% for overall prostate cancer and a detection rate of 40.1% for clinically significant prostate cancer.<sup>60</sup> Disadvantages of robot-assisted TP biopsy include long procedure times, the need for an operating room, and an increase in cost.<sup>60,61</sup>

## 4. Before and after freehand

A review of template-guided TP biopsy by Sivaraman et al has shown a diagnostic performance of 73–76% for the initial biopsy.<sup>62</sup> The upgrading/upstaging rate was 8–10% compared to 20–50% for TR biopsy.<sup>62</sup> However, the incidence of urosepsis was similar, acute urinary retention was more common, and the duration of the procedure was twice as long (45 to 60 minutes) as a TR biopsy.<sup>62</sup> There were a few other reviews before the freehand technique became common. However, those studies included biopsy performed with a fan technique. Thus, results could not be considered before the freehand technique review. Nevertheless, Xiang et al have found that there is no significant difference in diagnosis between a TP approach and a TR approach, with TP biopsy showing a lower risk of rectal bleeding and fever than TR biopsy.<sup>63</sup> Shen et al have found no significant difference in cancer detection rate or complications between the TP and TR approaches.<sup>64</sup>

Szabo's study of freehand biopsy has found an overall PCa detection rate of 45.5% and a rate of 25.1% for csPCa after excluding patients on active surveillance.<sup>57</sup> Overall, 10.2% of patients did not receive prophylactic antibiotics. However, there was no sepsis.<sup>57</sup> Fever occurred in only 0.5% of patients. There was no sepsis in biopsies performed under local anesthesia.<sup>57</sup> Acute urinary retention in 1.4%, growth hematuria in 16.0%, and perianal abscess in 0.008% were noted. However, there were no cases of morbidity.<sup>57</sup> In a study by Urkmez et al comparing freehand and template grid biopsy, it was found that cancer yield is similar, although urinary retention is lower in freehand biopsy.<sup>65</sup> In a study by He et al cancer detection

rates were similar between the freehand biopsy and the template grid biopsy.<sup>66</sup> Further research is needed to differentiate results based on the number of biopsy cores, anesthesia settings, and the freehand technique.

## 5. Prophylactic antibiotics

Since TP biopsy is considered a clean procedure, numerous studies have explored whether prophylactic antibiotics are necessary.<sup>67</sup> A systematic review and meta-analysis by Castellani et al have found no significant difference in the rate of postbiopsy infection or sepsis between those with the use of prophylactic antibiotics and those without using prophylactic antibiotics.<sup>68</sup> Similar results have been obtained even in studies where prophylactic antibiotics are not used for freehand biopsy.<sup>69,70</sup> After further large-scale research studies in the future, it will be possible to determine whether prophylactic use of antibiotics is necessary in TP biopsy.

## 6. Magnetic resonance image guided transperineal biopsy

MR-guided TP biopsy has been reported to have a better cancer detection rate for csPCa and anterior region PCa with fewer complications than MRI fusion TR biopsy.<sup>71</sup> MR-guided freehand perineal biopsy research is still predominantly focused on the fan technique. Wetterauer et al have performed an MRI cognitive freehand TP biopsy and found a cancer detection rate of 45.1% in PI-RADS 3, 62.2% in PI-RADS 4, and 93.7% in PI-RADS 5.<sup>72</sup> The MR Fusion freehand biopsy study conducted by Marra et al has shown an overall PCa detection rate of 43.9% and a csPCa detection rate of 39.4%, an acute urinary retention rate of 1.7%, and no case of sepsis.<sup>73</sup> Further evaluation of the MR-guided probe-mounted grid or cannula-freehand TP biopsy is needed.

## 7. Conclusions

The diagnostic landscape of prostate cancer has undergone significant transformation, with TR biopsy and TP biopsy playing central roles in the evolving diagnostic paradigm. TR biopsy has long been the established method for diagnosing prostate cancer. It provides a systematic approach to obtaining prostate tissue. However, its limitations including the risk of infection and potential rectal artery injury, have prompted a re-evaluation of its efficacy and safety. TP biopsy has witnessed innovations in the form of freehand techniques such as the fan technique, the probe-mounted grid, and the probe-mounted cannula. In addition, advances in anesthesia methods have made it possible to perform TP biopsy on an outpatient basis, thereby reducing patient discomfort. While both TR biopsy and TP biopsy have their merits, the latter offers certain advantages. By providing better access to the entire prostate and minimizing the risk of infection, TP biopsy addresses the limitations of TR biopsy.

## Conflicts of interest

There is no conflict of interest.

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