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PROSTATE CANCER (S PRASAD, SECTION EDITOR)

Should Transperineal Prostate Biopsy Be the Standard of Care?

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Abstract

Purpose of Review We reviewed the advantages and disadvantages of transperineal prostate biopsy (TP-bx) to evaluate its potential role as the standard of care for prostate biopsy.

Recent Findings Studies have suggested no difference in prostate cancer (PCa) detection rate between TP-bx and transrectal biopsy (TR-bx) but have suggested potentially increased detection of anterior prostate tumors. Advances in anesthetic technique have obviated the need for sedation thus allowing TP-bx to become an office-based procedure, which in turn can decrease the overall cost of TP-bx. Furthermore, given the low rate of infectious complications after TP-bx, some have foregone peri-procedural antibiotics without a change in the rate of infectious complications.

Summary Recent procedural advances have made TP-bx a tolerable, office-based procedure. Given the similar diagnostic performance and the benefits for the patient and community, TP-bx should become the standard of care for prostate biopsy for most patients. Future efforts should address the barriers for more universal adoption.

Keywords Prostate cancer · Prostate biopsy · Infection · Transperineal · Patient-centered outcomes

Abbreviations

AUR	Acute urinary retention
CI	Confidence interval
CI-PCa	Clinically insignificant prostate cancer
CS-PCa	Clinically significant prostate cancer
mpMRI	Multiparametric magnetic resonance imaging
OR	Odds ratio
PCa	Prostate cancer
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
TP-bx	Transperineal prostate biopsy
TR-bx	Transrectal prostate biopsy
TRUS	Transrectal ultrasound
UTI	Urinary tract infection
VAS	Visual analogue scale

Introduction

Prostate biopsy remains necessary for the diagnosis and treatment of prostate cancer. Biopsies are currently most often performed using a transrectal approach. However, prostate biopsy techniques have changed since inception, adapting to new technologies and discoveries, which now include the re-introduction of the transperineal biopsy (TP-bx). Currently, there is debate over whether transrectal biopsy (TR-bx) or TP-bx should be the standard of care.

Historically, the first prostate biopsies were performed using a transperineal approach, initially as an open surgery and then, after 1922, percutaneously [1]. Up until the 1950s, digitally guided TP-bx was most commonly performed, which was then replaced by digitally guided TR-bx, an approach that persisted into the 1990s [1, 2]. Transrectal ultrasonography (TRUS) was first used to augment the prostate biopsy technique in 1989; its use allowed for more accurate and less morbid procedures [1, 3]. TRUS remains indispensable for

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office-based biopsies. Next in the prostate biopsy continuum, urologists discovered that a 12-core sextant biopsy led to improved cancer detection rates when compared to a reduced number of cores, which ultimately lead the field to adopt biopsy templates that employ a minimum of 10–12 cores [4, 5]. The next step in prostate biopsy innovation came after the PROMIS trial supported multiparametric MRI (mpMRI) as a tool to increase the detection of clinically significant prostate cancer (CS-PCa) while decreasing the diagnosis of clinically insignificant prostate cancer (CI-PCa) [6]. With each of these innovations and discoveries, urologists were required to learn new skills to better patient care. Most recently, some urologists have abandoned TR-bx while adopting the transperineal route.

In this review, we will address the benefits and disadvantages of TP-bx. Specifically, we will focus on PCa detection rates, infectious and non-infectious complications, antibiotic stewardship, patient experience, the learning curve, and the associated costs; the synthesis of the above will support TP-bx as the new standard of care for most patients undergoing prostate biopsies.

Cancer Detection Rates

Much of the data supports equivalent cancer detection rates between TP-bx and TR-bx, with some early data suggesting higher rates of clinically significant prostate cancer detection with TP-MRI fusion when compared to TR-MRI fusion biopsy [7, 8, 9•, 10••, 11••]. Combined PCa detection rates (CS-PCa and CI-PCa) for systematic, and when indicated, targeted TR-bx range from 30.7 to 71.0% [6, 8, 12, 13]. Similarly, for TP-bx, PCa detection rates range from 42 to 67% [7, 12, 14–16]. The lower bound originates from a 2008 study suggesting that the total cancer detection rate with TP-bx is inferior (42.1% vs 48.3%, $p = 0.323$); however, this was not statistically significant [12]. In comparing systematic TR-bx and TP-bx, multiple studies including randomized controlled trials have found no differences in PCa detection rates between the two approaches (most recently TP-bx 50.4% vs TR-bx 47.3%, $p = 0.424$) [7, 8]. These data were further confirmed in a meta-analysis (relative risk (RR) of any cancer detection 0.94, 95% confidence interval (CI) 0.81–1.10) [9•]. In contrast to the studies that found no differences in cancer detection rates, a meta-analysis specifically addressing the detection of CS-PCa with MRI-fusion TP-bx and MRI-fusion TR-bx found higher cancer detection rates via the TP approach (RR 1.28, 95% CI 1.03–1.60) [10••]. Furthermore, a large multi-institutional retrospective study comparing MRI-targeted TP-bx and MRI-targeted TR-bx (MRI-fusion and cognitive fusion) found higher cancer detection rates with TP-bx (odds ratio (OR) of CS-PCa 1.19, 95% CI 1.12–1.50) [11••].

While overall cancer detection rates are similar, there may be some benefit to TP-bx in detecting anterior tumors, especially with the advent of multiparametric prostate MRI [10••, 11••, 17]. A study in 2012 determined a higher proportion of anterior tumors were detected by TP-bx compared to TR-bx (16.2% of exclusively anterior tumors vs 12.0%, $p = 0.046$), and these were detected at a smaller size and stage [17]. Similarly, a systematic review and meta-analysis of MRI-fusion TP-bx versus MRI-fusion TR-bx determined that anterior CS-PCa detection rates were higher with TP-bx (RR 2.46, 95% CI 1.22–4.98) [10••]. Most recently, a 2022 study showed that MRI-targeted TP-bx, when compared to TR-bx, detected more CS-PCa at the apex (OR 4.81, 95% CI 1.03–6.27), in the anterior prostate (OR 5.62, 95% CI 1.74–8.13), and in the transition/central zone (OR 2.67, 95% CI 1.42–5.0) [11••]. Despite the possible benefit in diagnosing anterior tumors using TP-bx, some urologists report difficulties using the TP approach in patients with a larger prostate and/or a narrow pelvis. With recent technical developments, however, some have anecdotally suggested that using a transperineal access system as opposed to a grid may help overcome these challenges.

Infectious Complications and Antibiotic Stewardship

Infectious complications of prostate biopsy with standard prophylactic antibiotics have risen, leading urologists to develop new approaches to prophylaxis [18–22]. The rise in infectious complications is likely secondary to antibiotic resistance as the higher infectious complication rate is associated with an increase in antibiotic-resistant Enterobacteriaceae, including fluoroquinolone-resistant *E. coli* [21, 23–25]. In fact, the degree of fluoroquinolone-resistant *E. coli* between 2003 and 2006 was associated with specialty-specific prescription patterns at one Dutch hospital, with urology having the highest antibiotic prescription rate and resistance to fluoroquinolones [25].

In response to rising rates of infectious complications, two main prophylactic strategies have emerged: targeted prophylaxis and augmented prophylaxis. Targeted prophylaxis involves collecting a preprocedural rectal culture and targeting the prophylactic antibiotic to the culture results. An initial study evaluating the efficacy of targeted prophylaxis demonstrated that despite 19.6% of patients harboring fluoroquinolone-resistant organisms, targeted prophylaxis decreased post-biopsy infectious complications, although this was not statistically significant (targeted prophylaxis 0% vs control 2.6%, $p = 0.12$) [26]. This finding prompted later studies and a meta-analysis, which demonstrated a statistically significant higher rate of infectious complications when using empiric as opposed to targeted prophylaxis (RR 1.81, 95% CI 1.28–2.55) [27•, 28–33]. In

contrast to targeted prophylaxis, augmented prophylaxis typically adds a second, often more broad-spectrum antimicrobial to the peri-procedural antibiotic regimen. Bloomfield et al. demonstrated augmented standard ciprofloxacin prophylaxis with a single dose of ertapenem and showed a decrease in all infectious complications (from 2.65 to 0.34%; risk ratio 0.13, 95% CI 0.06–0.27) and bacteremia (from 1.14 to 0.04%; risk ratio 0.04, 95% CI 0.01–0.22) [34]. Similarly, augmenting standard ciprofloxacin with ceftriaxone decreased hospitalizations for post-biopsy infections (from 0.6 to 0.0%, $p < .0001$) [35]. The efficacy of these two strategies was further supported by implementing them across the Michigan Urological Surgery Improvement Collaborative's participating practices (individual practices chose which strategy to follow), which resulted in a decrease in post-biopsy infection-related hospitalizations (from 1.19 to 0.56%, $p = 0.002$) [36].

In contrast to the TR-bx technique, which requires antibiotics for acceptable levels of infectious complications, the reintroduction of TP-bx has been accompanied by an often lower rate of infectious complications when compared to TR-bx, even without antibiotics. TP-bx distinguishes itself from TR-bx from an infectious standpoint given the very nature of avoiding the rectum, which reduces the bacterial load on the biopsy needle as it pierces the prostate [37, 38]. While one early meta-analysis demonstrated no difference in sepsis rates between TP-bx and TR-bx (2/497 vs 2/472, respectively, $p = 0.936$) nor a significant difference in rates of fever (1/447 vs 7/435, respectively, $p = 0.073$), this study remains an outlier in its findings [39]. Many other large series demonstrated reduced infectious complications after TP-bx when compared to TR-bx [39–41]. One large analysis of 73,630 biopsies determined that TP-bx was associated with a lower rate of readmission secondary to sepsis (1.0% vs 1.4%; adjusted risk difference −0.4%, 95% CI −0.6 to −0.2) [41]. A similar outcome was described in another large study ($n = 4233$ biopsies) where TP-bx resulted in no patients with bacteremia, no patients requiring hospitalization for complications, and was associated with a lower risk of all infectious complications when compared to TR-bx (adjusted odds ratio 0.28, 95% CI 0.08–0.68) [40]. Separating urinary tract infection (UTI) from sepsis, a 2022 study determined that TR-bx had a higher risk of both UTI and sepsis when compared to TP-bx (RR of sepsis 3.65, 95% CI 1.21–11.03; RR of UTI 3.04, 95% CI 1.07−8.66) [7]. The lower incidence of infectious complications and the nature of the TP-bx not going through the rectum has driven some to omit prophylactic antibiotics with the resultant infectious complications still nearly non-existent. In one retrospective cohort of 184 patients undergoing TP-bx without prophylactic antibiotics, there were no cases of sepsis and only two cases of afebrile UTIs [42]. In another, antibiotic prophylaxis prior to TP-bx was not associated with a lower risk of sepsis (RR 0.78, 95% CI 0.13−4.63) or UTI (RR 1.17, 95% CI 0.24−5.74) [7]. Similarly, two recent systematic reviews and meta-analyses comparing TP-bx with and without antibiotic prophylaxis found no difference in rates of sepsis (with antibiotics 0.05% and 0.13% versus no antibiotics 0.08% and 0.09%, $p > 0.05$ for both reviews) or overall infections (RR 2.09, 95% CI 0.54–8.10 and RR 1.11, 95% CI 0.84–1.46) [43, 44••]. Recently, a randomized controlled trial (RCT) of 555 patients undergoing TP-bx with or without the use of prophylactic antibiotics demonstrated no hospitalizations for sepsis or UTI in either group. There was, however, a non-significantly higher risk of UTI in the group without prophylaxis (1/277 receiving antibiotics vs 3/276; absolute difference 0.73%, 95% CI −1.08 to 2.81) [45••].

TP-bx has the potential to decrease and nearly eliminate the use of prophylactic antibiotics for prostate biopsies, thus reducing the contribution of prostate biopsies to antibiotic resistance [46, 47]. While the targeted and augmented prophylactic antibiotic approaches have decreased post-biopsy infectious complications, there is concern over the contribution of continued antibiotic use prior to prostate biopsy on the emergence of resistant organisms and their subsequent infections, especially if using broader-spectrum antibiotics [22, 48–50]. Antibiotic resistance develops in association with microbial exposure to antibiotics and, while necessary for TR-bx, likely contributes to increased resistance [48–50]. The suggested use of carbapenems to augment prophylaxis furthermore runs contrary to the Center for Disease Control recommendation to avoid carbapenems when possible given the urgent threat level (highest) of carbapenem-resistant Enterobacteriaceae, which cost 1100 lives and $130,000,000 in 2017 in the USA [51].

Non-Infectious Complications

While infectious complications remain the most distinctive difference between TP-bx and TR-bx, urologists should consider other complications of prostate biopsy including acute urinary retention (AUR), rectal bleeding, hematuria, erectile dysfunction, and vasovagal/syncopal events. Some suggest increased rates of AUR with TP-bx when compared to TR-bx [52–54]. However, this increased rate may be an artifact of the number of biopsy cores rather than the method of biopsy. Other recent studies, in which the number of cores is comparable to TR-bx, have reported similar rates of AUR (2.15–5.0% for TP-bx vs 2.46–6.3% after TR-Bx, $p > 0.05$ in all studies) [7, 10••, 55]. TP-bx has lower rates of rectal bleeding (RR 0.02, 95% CI 0.01–0.06) and similar rates of hematuria (RR 0.79, 95% CI 0.63–1.01) [8, 9•, 55]. The impact on erectile function also appears similar between both approaches. After both TR-bx and TP-bx, there is a significant decrease in erectile function, as measured by the International Index of Erectile Function score, without a difference between the two approaches; the reduced erectile dysfunction appears to resolve in 3 months [56–58]. Furthermore, some suggest

an increased risk of syncopal/vasovagal events after TP-bx; however, published data support a similar range between both approaches, from 0.6 to 0.9% after TP-bx compared to 0.05% to 1.2% after TR-bx [8, 59, 60].

Patient Experience and Pain

Many studies demonstrate that when comparing TP-bx and TR-bx under local anesthesia, patients undergoing TP-bx are more likely to experience pain, and that the pain is worse. However, techniques to improve analgesia during TP-bx have been introduced and continue to evolve. These new techniques have contributed to a significant reduction in pain, resulting in the TP-bx now being fairly well-tolerated with a similar impact on quality of life (QOL) as TR-bx [61]. An early (2015) study comparing pain during TP-bx and TR-bx performed under local anesthesia determined that in the TP-bx group, the pain intensity was twice that of the TR-bx group, albeit the reported pain was mild (median visual analogue scale [VAS] score 4.0 vs 2.0, $p < 0.001$); the difference was driven by the infiltration with local anesthesia [8]. A review also concluded that there was a higher chance of feeling any pain during TP-bx (RR 1.83, 95% CI 1.27–2.65) [9•]. Similar pain scores between TP-bx and TR-bx in another study underline that with good anesthetic technique, the difference in pain can be substantially decreased and possibly even eliminated (mean VAS score 1.56 vs 1.42, respectively, $p = 0.591$) [62]. In fact, in a prospective study of 1218 patients who were surveyed on their experience with TP-bx, only 5.6% believed it caused significant enough pain to necessitate general anesthesia [16].

Techniques to improve analgesia during TP-bx continue to evolve [8, 9•, 61]. The pain generated during TR and TP biopsies shares some similarities given the use of the TR ultrasound probe and piercing of the prostatic capsule but is differentiated by the TP-bx uniquely causing pain through the sensors at the perineal skin and the structures superficial to the prostatic capsule (innervated by the pudendal nerve) [63]. These pelvic innervation patterns differentially contribute to the discomfort patients feel during the TP-bx procedure and have led to the development of directed anesthetic techniques [8, 64, 65••, 66]. Understanding which parts of the biopsy the patient finds most uncomfortable allows urologists to address them with new techniques. Multiple studies of TP-bx performed under local anesthesia have demonstrated that patients report the most pain during the administration of local anesthesia and the least during probe placement [15, 64, 66]. The unique pain of local anesthesia raises the possibility of decreasing the maximum pain level by buffering the local anesthetic with sodium bicarbonate, which has been shown to decrease pain levels in both breast biopsies and hand surgery [67–69]. One study performing a peri-prostatic block and skin infiltration of buffered local anesthesia found excellent pain control comparable to that reported for TR-bx and the most effective techniques for TP-bx (median VAS score 2) [15]. In a RCT comparing three anesthesia methods, the best pain control was provided with local infiltration of the skin and a pelvic plexus block (mean VAS score 2.1) [65••]. Regardless, most studies have found that with current analgesic techniques, most men have adequate pain control during TP-bx with pain scores in the mild range [14, 64, 66]. Furthermore, the use of a transperineal access system avoids multiple skin punctions (compared to one puncture per biopsy with a grid) and has also been associated with decreased pain scores (mean whole procedure VAS score 2.20 vs 2.90, respectively, $p < 0.01$) [70]. Studies further suggest that patient characteristics, such as anxiety level, are associated with pain level during both TP-bx and TR-bx [64, 71]. Despite the widespread tolerability of TP-bx, just as with TR-bx, there are patients that will require sedation to undergo the procedure. Contemporary data, however, support that both TR-bx and TP-bx are well-tolerated under local anesthesia, obviating the need for sedation for most, regardless of the technique.

Additional research into novel techniques for pain control will only further improve the patient experience.

Learning Curve

Some contend that the learning curve may be longer with TP-bx when compared to TR-bx. However, the difference might not be significant. Prior work suggests that it takes roughly 12 procedures to perform a high-quality systematic TR-bx [72]. Similarly, initial data suggests that high-quality TP-biopsies are achieved after 15 procedures [73].

There are more published data on the learning curve for MRI-fusion TP and TR-bx techniques. These data suggest that the learning curve for the TP-MRI fusion technique is not prohibitive and can be augmented by structured training protocols. The learning curve for MRI-fusion TR-bx ranges from 82 to 109 biopsies, depending on the outcome measure used to evaluate the learning curve [74–76]. Formalized training shortens the learning curve for MRI-fusion TP-biopsies. In one urologist's experience with no formalized didactics, the procedure time and PCa detection rate were optimized after 119 and 124 biopsies, respectively [76]. In a study assessing junior residents' performance after a 2-week training period followed by approximately 84 independently performed biopsies, there was no difference in PCa detection or patient pain when compared to the attending physician; the residents, however, did take longer to perform the procedure (16 min versus 19.7–20.1 min, $p < 0.001$) [77]. In another study of residents undergoing a rigorous MRI-fusion TP-bx and systematic TP-bx training program, the residents

achieved PCa detection rates comparable to published norms after 10 training biopsies and approximately 37 independently performed biopsies [78•]. While concerns over the learning curve persist, structured training protocols might hasten urologists' progression and learning and render the learning curves for TP-bx and TR-bx similar.

Procedure duration is also referenced when discussing learning curves. Published procedure durations for MRI-fusion TR-bx have ranged from 14.73 to 24.0 min, and for MRI-fusion TP-bx, they have ranged from 14.4 to 22.5 min [8, 75–77, 78•, 79]. The considerable overlap between the methods likely reflects the heterogeneity of the biopsy technique, anesthetic method, and operator characteristics, raising questions about the generalizability of published values. Ultimately, to better analyze the learning curve and procedure times, newer studies are needed using modern techniques and training programs.

Associated Costs

Three distinct cost categories must be considered regarding TP-bx in comparison to TR-bx: capital costs to be able to perform TP-bx, procedural costs, and downstream costs.

Capital costs include the non-consumables required to perform TP-bx. At a minimum, the facility needs an exam bed and stirrups to achieve lithotomy position, a transrectal ultrasound probe adequate for TP-bx, and an ultrasound machine. In order to perform software-based MRI-fusion TP-bx (currently performed by approximately 58% of urologists in the USA), the facility also requires the necessary commercial hardware, which can be purchased or rented [80]. Furthermore, costs related to lost productivity and training must be considered.

Procedural costs include personnel and physician fees and consumables, some of which are specific to TP or TR biopsy. Performing TP-bx under general anesthesia/sedation has traditionally kept the TP-bx procedural costs higher than TR-bx; however, the recent introduction of performing TP-bx under local anesthesia removes these anesthesia-related costs [81, 82]. There are other procedural costs which are specific to TP-bxs, such as a transperineal access unit (e.g., the FDA-approved PrecisionPoint™ Transperineal Access System, which retails for an estimated $200) or a biopsy grid. However, some clinicians are using a lower-cost alternative (e.g., a 14-g peripheral IV catheter), and other potentially lower-cost options including non-disposable guides are being developed (e.g., the Cambridge Prostate Biopsy Device, SureFire™). Cost savings for TP-bxs potentially lie in omitting prophylactic antibiotics and stool cultures.

Finally, downstream costs of prostate biopsy should include costs of complications, which, as previously described, vary in magnitude by the biopsy approach. In one example, the cost of treating post-biopsy sepsis has been estimated between $8672 and $19100 per episode in the USA [83]. One study found that when including complications in their cost analysis, TP-bxs were associated with a lower cost for the health system when compared to TR-bx [55]. Treating non-infectious complications incurs other costs (e.g., with associated unplanned clinic or emergency department visits) and should be included in calculations.

Cost calculations are complicated given the immediate and potential downstream impacts of cost. Furthermore, costs may have differential impacts on various stakeholders. For practices not yet equipped to transition to TP-bx, up-front capital costs can be significant; these costs are not reimbursed and could disincentivize and/or limit a practice's ability to transition to performing TP biopsies. On the other hand, costs of complications currently impact healthcare payers and patients (through copayments and premiums), yet they do not currently directly affect the proceduralist. The interplay of these costs provides an opportunity to implement system-based changes that incentivize involved parties to adopt TP-bx whether it be by increasing reimbursements for TP-bx or bundling prostate biopsies to their complications.

Conclusion

Recent data and advancements in technique suggest that TP-bx may now be superior to TR-bx for most patients undergoing prostate biopsy. The data comparing TP-bx present a similar cancer detection rate to TR-bx, with the potential of TP-bx allowing for a better sampling of the anterior prostate. Infectious complications are nearly avoided with TP-bx, and one can safely omit antibiotics in many patients thus not further contributing to antibiotic resistance. TP-bx has a non-infectious complication profile that is similar to TR-bx. While many studies report worse pain scores with TP-bx under local anesthesia when compared to TR-bx, with the introduction of new anesthetic techniques, this pain level is tolerable, and the procedure is frequently performed in a clinic using local anesthetic. The learning curve for TP-bx should not preclude implementation given its similarity to TR-bx. Once the initial capital costs required to perform TP-bx are surpassed, the procedural costs are similar with modern techniques, and there are potential savings at a system level by avoiding costly complications. On the road to better diagnose prostate cancer, urologists have adapted new technologies and protocols to better serve our patients; recent data support a return to TP-bx as the next step in this prostate biopsy evolution.

The question remains, "should TP-bx be the standard of care?" The answer is "yes." TP-bx should be the standard of care for most patients. This does not discredit, however, the significant capital investment and training which will be required to make this become the standard of care, and there will still be some patients for whom TP-bx is not optimal. Additional

research should evaluate methods to improve patient tolerability and identify barriers and facilitators to universal adoption (e.g., capital costs, cost of consumables, education).

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Declarations

Conflict of Interest Dr. Wilcox Vanden Berg has nothing to disclose. Dr. George reports Philips Medical—Research agreement. Dr. Kaye reports personal fees from Janssen Pharmaceuticals, outside the submitted work.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were performed in accordance with all applicable ethical standards including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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