Hundred years of transperineal prostate biopsy

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***Abstract*:** The earliest recorded efforts to biopsy prostate, in the early 20th century, were made through transperineal (TP) approach, with open perineal prostate biopsy (PBx) being considered the gold standard for prostate cancer (PCa) diagnosis in that era. Later, to minimize morbidity and increase diagnostic accuracy, several technical modifications and transrectal ultrasound (TRUS) assistance were incorporated. However, in the 1980s, the transrectal (TR) approach became the predominant PBx method following the introduction of TRUS-TR PBx with sextant sampling, providing a convenient and efficacious method for prostate sampling. With modernization of PCa diagnosis, a recent resurgence of the TP PBx has been observed, driven primarily by TR drawbacks of infectious complications and sampling limitations. TP PBx is rapidly emerging as the new PBx standard, being officially recommended as the initial approach for biopsy in Europe and is increasingly being conducted and studied in the United States. The modern era of TP PBx is based on the improvements in local anesthesia techniques, TP access systems, and robotic assistance. These modifications and advancements have improved the ease of use, patient comfort, and diagnostic outcomes with TP PBx. Herein, we present a history of the evolution of TP PBx spanning over 100 years and explore the basis of the technique that merits future utilization.

Keywords: prostate biopsy, transperineal, prostate cancer, prostate, urology

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Introduction

Prostate cancer (PCa) remains the most common non-cutaneous malignancy in men, with an estimated incidence of 1,414,259 cases worldwide and accounting for 7.3% of all cancers in 2020.[1] Since the early 20th century, prostate biopsy (PBx) has been used to pursue clinical suspicion of PCa. Approximately one million prostate biopsies are performed per year in the United States alone, and there has been substantial investigation into methods to best obtain an accurate histopathologic diagnosis while minimizing morbidity.[2]

The two contemporary approaches to perform prostate biopsies (PBx) include the transrectal (TR) PBx and the transperineal (TP) PBx. Beginning in the 1920s, PBx was initially performed *via* the TP approach due to concern for fecal contamination during TR approach that rendered physician opinion of latter technique as unsafe.[3] However, since the 1980s, TR has become the predominant approach for PBx due to the development and popularity of transrectal ultrasound (TRUS) and ease and convenience of this approach. Over the past few years, there appears to be a reversion to TP PBx secondary to the development of new techniques and technology facilitating TP approach and data implicating limitations and risks of TR PBx. There is a clear evidence of greater risk of infection and sepsis with TR PBx[4–18] compared to TP PBx.[19,20] Furthermore, studies have demonstrated that TP PBx provides more than adequate core lengths and better sampling of the apex and anterior prostate.[21]

With modernization of PCa diagnosis, an international resurgence of TP has been observed. The objective of the following review is to present the

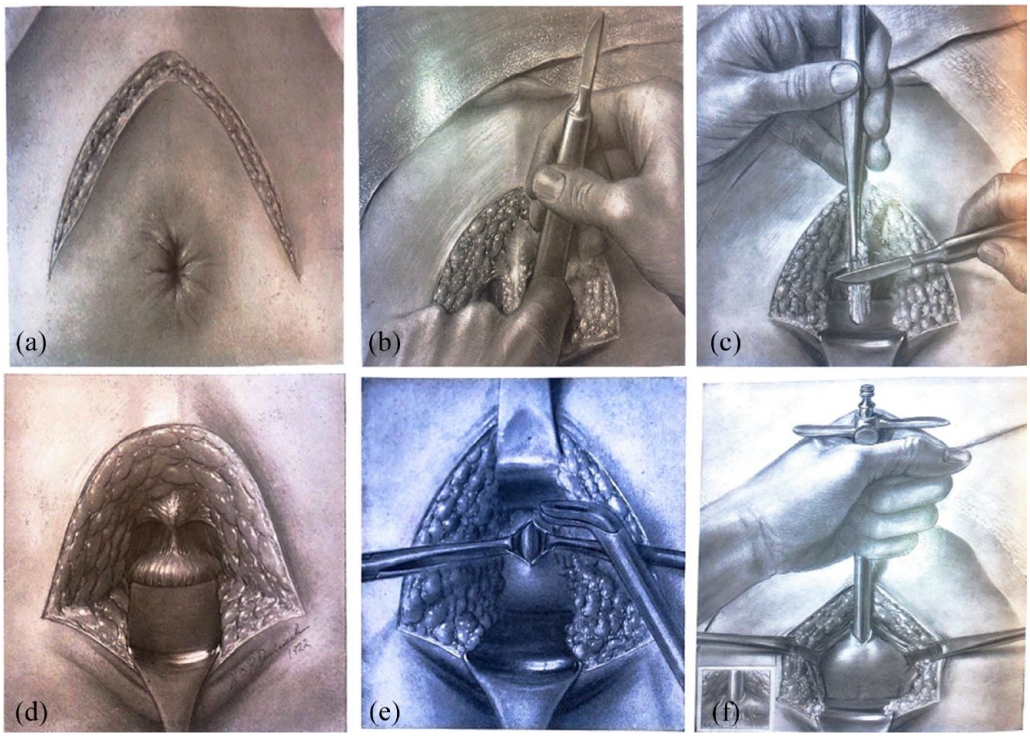

Figure 1. Illustrations from Young's Practice of Urology (1926)[25] describing the process of open perineal prostate exposure, used primarily for prostatectomy but also could be used for PBx: (a) perineal incision, (b) blunt dissection on either side of central tendon, (c) division of central tendon, (d) central tendon divided to expose recto-urethralis, (e) membranous urethra exposed, and (f) tractor drawing prostate down to expose prostate covered with anterior Denonvilliers' fascia, allowing for suspicious lesion biopsy. (Public Domain as of 1 January 2022).

evolution of TP PBx from the inception of PBx to the modern day spanning almost a 100 years. First, early efforts to best obtain adequate prostate tissue transperineally in early 1900s are described. Next, discussions on the rise of the TR PBx, followed by the limitations of the TR PBx are described. Finally, advancements in technique, application, and technology leading to the modern era of TP PBx and contributing to its rise are explored.

Early efforts to transperineally biopsy the prostate

Origins

The first reported efforts to perform PBx occurred *via* the TP needle punch biopsy in 1922 by Benjamin Barringer at Memorial Hospital in New York. This approach used screw tip needles to execute perineal punch biopsies. Although the technique was minimally invasive, it demonstrated limited success, with only 50% (16/33 subjects) of biopsies successfully retrieving diagnostic prostate tissue.[22–24]

In 1926, Hugh Hampton Young, regarded as one of the Fathers of American Urology, published his open perineal technique as an effective method of performing PBx[25] in *Young's Practice of Urology*.[25] His description of the procedure read as follows:

> a transverse incision was made between the ischial tuberosities and 2 cm above the anus (Figure 1(a)). Blunt dissection was used to access the prostate through the ischiorectal fossa (Figure 1(b)), followed by transection of the central tendon of the perineum (Figure 1(c)), and exposure of the recto-urethralis muscle and prostate capsule (Figure 1(d)–(f)).

Suspicious areas of the prostate were grasped with forceps and wide, deep excisions were performed. Frozen tissue sections were sent for analysis with up to 95% accuracy. If a histopathologic diagnosis of PCa was likely, the surgeon would then complete a prostatectomy. While accurate, the open perineal PBx was only attempted if the patient consented to prostatectomy. Despite its accuracy, the open perineal PBx technique carried a

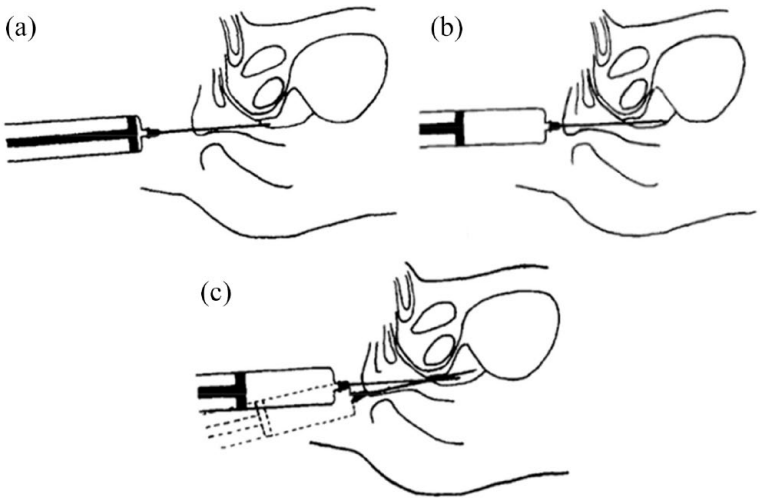

Figure 2. Ferguson's illustration depicting the technique used for TP needle aspiration of the prostate. (a) Needle within the capsule with syringe closed. (b) Plunger pulled as needle advanced into suspected prostatic tissue. (c) Angling of needle to cut off plugged tissue. Following the cutting off plugged tissue, the needle is withdrawn. Permission for use granted by Elsevier, License number 5206040909934, 11 December 2021.

considerable risk of side effects, including erectile dysfunction, urinary incontinence, and rectal injury. In addition, Young's technique was invasive, required induction and risks of general anesthesia with up to a week of hospitalization.[3,22,25]

Minimally invasive approach

To manage clinical suspicion of PCa in a less invasive and safe manner, minimally invasive techniques were further pursued. Elaborating on Barringer's 1922 perineal punch biopsy technique[23] and utilizing techniques from Martin and Ellis,[26] Russel Ferguson, another urologist at Memorial Hospital, NY, developed a modified TP needle aspiration method in 1930.[22,27] For Ferguson's PBx, the patient was placed in lithotomy position, and the perineum was prepped with ethanol. Local anesthesia was administered to the perineum and into the prostate capsule under the guidance of digital rectal exam (DRE). A sterile reusable glass syringe[28,29] with a 4–6 inch long 18-gauge needle was inserted into the perineum and advanced with the syringe closed DRE. When the suspected area of PCa was reached, the plunger of the syringe was drawn to create a vacuum for tissue acquisition (Figure 2). Following withdrawal of the biopsy needle, the tissue sample could be transferred onto a slide for microscopic analysis. A series of 280 patients undergoing this procedure was first published by Ferguson *et al.* in 1930 and demonstrated 78–86% of the cases obtaining adequate prostate tissue.[22,27] Although the Ferguson series provided some enticing evidence for TP needle aspiration, its use declined in the 1940s ultimately due to unsatisfactory tissue for diagnosis[27,30] and the simultaneous promising results for TR approach.[3,4,16,24]

In 1954, Kaufman University of California, Los Angeles (UCLA) emphasized that an abnormal DRE merits histologic confirmation if PCa was suspected. At the time, TP needle or punch biopsy of the prostate, limited by the aforementioned challenges, was never widely adopted and open perineal biopsy was the only reliable option for tissue diagnosis of PCa. Kaufman evaluated the efficacy of needle biopsy, along with DRE and Papanicolaou smear, as a method of diagnosing PCa compared to open perineal or transurethral PBx. Kaufman performed the needle biopsy by palpating a suspected area on DRE and using a digit to guide a VIM-Silverman needle transperineally just 1 cm anterior to the anus and capture multiple cores of tissue (Figure 3).[31,32] Results of Kaufman's work demonstrated that DRE was capable of detecting PCa and that a prostate needle biopsy could confirm the diagnosis with up to 86% accuracy.[3,32] Parry and Finelli[31] conducted a study in 1960 with the same method of TP PBx and showed satisfactory results.

Kaufman's PBx technique provided other advantages as well, such as permanent tissue sampling, a technique that could be performed in the office under local anesthesia, indication for certain

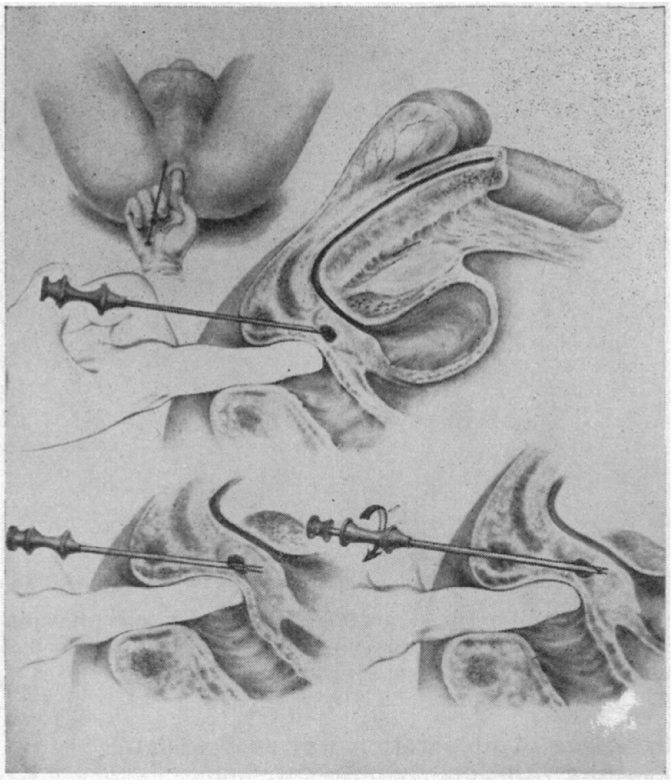

Figure 3. Artist's illustration of technique used by Kaufman et al. A digit inserted rectally guided a transperineally inserted needle to a suspicious prostate nodule32 (permission granted by the BMJ).

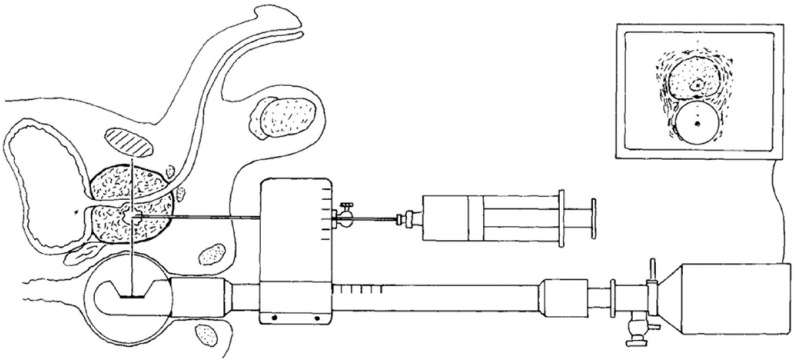

Figure 4. Illustration of the setup used by Holm *et al.* for TRUS-guided placement of the needle for TP PBx. Permission for use granted by Wolters Kluwer Health, Inc., License number 5145320111525, 10 September 2021.

palliative therapies if positive and allowed for repeat biopsy feasibility within 2–3 weeks if the initial biopsy was negative. Unsurprisingly, this technique was found to be safer than open technique with reduced risk for erectile dysfunction, rectal injury, and urinary incontinence. However, both Kaufman and Parry emphasized that needle PBx could not completely rule out PCa and was inferior to open perineal PBx.

Imaging assistance

Beginning in 1963, Takahashi popularized TRUS imaging of the prostate revolutionizing the diagnosis of PCa.[22,24,33] In 1965, Gotoh and Nishi[34] were the first to use TRUS in an effort to diagnose PCa. By 1985, ultrasound probes with at least 5 MHz frequency were developed and were commonly used for ultrasound prostate imaging.[35]

The initial clinical use of TRUS for PBx occurred with a TP approach in 1981 by Holm and Gammelgaard *et al.* Their results demonstrated satisfactory cancer detection and minimal complications in 16 patients with clinical suspicion of PCa. For the TRUS-guided TP technique, the patient was positioned in lithotomy, the perineum was prepared and draped in sterile fashion, and local anesthetic was administered to the perineal skin and prostate. A TR probe with a rotating handle, needle guide plate, and limiting knob were used to help safely perform the biopsy. The ultrasound probe was inserted into the rectum, and adjustments were made until suspicious areas were identified using a needle guide on the screen. The suspicious area was biopsied and from the contralateral lobe, regardless of its ultrasonic appearance. If there were no suspicious areas, a biopsy was obtained from each lobe. A small incision in the skin was made to ease passage of the biopsy needle to complete the TP PBx (Figure 4).[36,37]

Just 8 years after the TRUS-TP PBx technique, the best reflection of the most common modality for PBx today, the TRUS-TR PBx, was established by Hodge *et al.* in 1989. Their results demonstrated finding cancer in 53% of the time in patients with previously negative finger-guided biopsies ($n = 43$) and confirming previously diagnosed cancer in 94% of subjects.[38,39] In the same year, Hodge *et al.* published findings on systematic sampling.[39–41] In what would become known as the sextant technique, biopsy cores were taken from six regions of the prostate: apex, middle, and base of each lobe parasagitally in addition to any hypoechoic lesions identified on ultrasound. Results showed that the sextant method detected 9% more PCa[3,22,24,41] and ensuing research regarding systematic schemes supported the modern standard of a 10–14 core regimen with additional targeted biopsies to maintain diagnostic accuracy while minimizing complication risk.[42,43] Although the first TR PBx efforts using finger-guided approach were described in 1937 by Astraldi *et al.*[4] and involved a finger-guided approach, it was not until these landmark publications by Hodge *et al.* providing evidence for TR PBx efficacy and convenience that allowed for it to become the standard for PBx[40] and for TP biopsies to fall nearly obsolete.

Brachytherapy grid

Over the years, improvements in ultrasound technology, increased physician understanding of the sonographic appearance of potential PCa (i.e. 90% hypoechoic),[35,39,44,45] and novel ultrasound probe accessories (e.g. a spring-loaded biopsy ultrasound attachment) have further facilitated TRUS-guided TP biopsies.[24,35,39,46] Another important development occurred in 2003 by Barzell and Whitmore,[47] in which a brachytherapy grid dividing the prostate into 24 zones was used to perform TP PBx. The grid helps ensure precise systematic sampling of the prostate for precise biopsy localization and reduced human error.[48] The template mapping biopsies, using brachytherapy grid, spaced at 5-mm intervals throughout the prostate were found to have an overall detection rate of 95% for lesions at least 0.125 cm^3,[49] proving non-inferior compared to TR PBx.[50]

Rationale for TP PBx: limitations and pitfalls of TR approach fueling the resurgence of TP PBx

Today, TRUS-TR PBx is still the predominant technique to diagnose PCa with over 2 million TR biopsies performed per year in North America and Europe.[18,51] Over the last several years, research into TR route for PBx has revealed several concerns associated with this approach.

The primary concern with TR approach is the risk of post-TR infection or sepsis. Post-TR infection rates are increasing despite routine antibiotic prophylaxis (i.e. fluoroquinolones) and escalating antibiotic choice (i.e. carbapenems).[51] A 2011 study involving 5% random sample study of Medicare patients from 1991 to 2007 found a 6.9% hospitalization rate within 30 days after a PBx, with statistically significant increasing infectious hospitalizations in more recent years.[11,52] Other estimates suggest as high as 10% and 0.13% for post-TR infection and post-TR urosepsis mortality rate, respectively.[51] A 2021 meta-analysis analyzed TR PBx technique modifications and their effect on infection rates, such as number of cores taken, needle size and type, and enema or antiseptic preparation. Rectal preparation with povidone-iodine, along with conversion to a TP approach, was the only modification found to significantly reduce TR PBx infection rates in this analysis.[53] Other success reducing TR PBx infectious complications and morbidity has been found by altering antibiotic prophylaxis regimens, such as targeted (*via* rectal swab cultures)[54] and augmented approaches.[55]

In comparison, single-center experiences have published post-TP sepsis and infection rates ~0% and <1–2%, respectively.[19,56–59] Meta-analyses have found similar results, reporting negligible rates of post-TP-infection,[60] 3–4x higher odds for infectious complications following TR PBx, and lower risks of fever and rectal bleeding.[57,61,62] The reduction in infectious risk with TP PBx has been the most important advantage of this approach and has served as the primary driver of the increasing popularity of this approach. In addition, TP PBx can be performed with none or only one dose of antibiotics which can decrease the impact of peri-biopsy antibiotics in fueling antibiotic resistance in rectal flora. Although improved infection rates, TP PBx is not without its complications with acute urinary retention (AUR) being the most cited concern. AUR rates have been reported around 1–11% following TP PBx.[63–67] AUR rates appear to be positively correlated with larger prostates, increased number of biopsy cores (i.e. mapping), and general anesthesia use.[64,66] It is estimated that TP PBx, in 278 patients, would prevent one sepsis readmission at the cost of three AUR readmissions.[66] Although a risk of readmission does exist, the average length of stay is reportedly shorter in men who have undergone TP PBx as compared to TR PBx indicating less severe complications.[66]

Diagnostically, TR biopsies have demonstrated high rates of false negatives (up to about 50%)[62] and undergrade PCa about 25% of the time.[68] Although in terms of overall cancer detection for a biopsy-naïve patient, TP and TR PBx are seemingly comparable;[57,62,69,70] TP appears to detect more PCa in patients undergoing re-biopsy or active surveillance, suggesting an increased ability of TP to detect clinically significant PCa certain subsets.[70] A study done at John's Hopkins in men undergoing active surveillance for PCa demonstrated a statistically significant upgrading to clinically significant cancer in men undergoing TP biopsy compared to TR biopsy.[71] Pepe *et al.* compared mpMRI/TRUS TP cognitive PBx *versus* mpMRI/TRUS TR fusion. Compared to TR, TP was able to detect more clinically significant PCa (CSPC; 93.3% *versus* 66.7%) and TP was able to detect cancer on smaller mpMRI lesions (13 *versus* 10 mm). Furthermore, TP was able to detect 93.7% of the PCa located in the anterior zone *versus* a 25% detection rate for TR.[72] Confirmed by other studies, the ability of TP PBx to detect CSPC is attributed to better sampling of the anterior and apical zones of the prostate, improving the detection of likely nonpalpable PCa.[21,71,73,74]

The improved detection of CSPC in TP PBx compared to TR PBx emphasizes the importance of its use in patients with suspected PCa but a negative prior TR PBx. TP PBx has also demonstrated clinical utility when PCa is suspected but mpMRI is negative, as evidenced by Artiles Medina *et al.*[75] finding TP saturation biopsy can detect PCa in 50% of patients with a negative mpMRI but PCa is suspected. In addition to scenarios when magnetic resonance imaging (MRI) is failing to detect the PCa, TP PBx is increasingly being encouraged over TR PBx for biopsies in patients with high-grade Prostate Imaging Reporting and Data System (PI-RAD) lesions to ensure detection of CSPC and to obtain better PCa localization for potential treatment options (i.e. focal therapy).[76]

Evidence of shift to TP biopsy in clinical practice

In recent years, there has been an accumulation of data displaying and encouraging a shift toward TP biopsies. One of the more well-known examples of this is the 'TRexit' movement by the urologists at Guy's Hospital in London. In 2017, the group made a 'clean break' from TR biopsy and solely performed TP biopsy after reviewing data on infection rates. After making the change, 678 TP biopsies over the next year were performed with only three separate instances of sepsis, urinary tract infection, and hematuria postoperatively and 60% of the TP biopsies required solely local anesthesia.[59] This initiative was continued by the South East London Cancer Alliance, and by 2019, they had successfully ceased all TR biopsies in six hospitals serving 1.5 million people across the United Kingdom. Through training and resource allocation, this feat was accomplished and they aim to phase out TR and replace it with TP across the United Kingdom by 2022.[51] More recently, the 2021 European Association of Urology guidelines recommend TP as an initial approach for PBx if feasible.[77]

The TP movement, well underway in Europe, has gained traction and has increasingly become a part of clinical practice and clinical trials in North America. From 2009 to 2015, Liu *et al.*[78] studied private insurance claims and identified

biopsy-naïve men undergoing TP biopsies at a rate of ~0%; however, in 2018 and 2019, a Pennsylvania Urologic Regional Collaborative found rates of TP PBx in biopsy-naïve men had increased to 1.2% and 2.9%, respectively.[79] With evidence of increased use clinically, as of the year 2021, clinical trials are being conducted and published to further validate TP PBx, justify costs, and increase patient experience. Albany Medical Center is conducting a randomized trial of 568 randomized 1:1 TR or TP to study infectious and bleeding complications.[80] In the Ottawa Hospital, a similar randomized control trial with 360 men is again looking at infection rates and clinically significant PCa detection differences.[81] Furthermore, the largest ongoing multi-center randomized control trial with 1302 patients is occurring at Weill Medical College of Cornell University to better evaluate in-office TP MRI-targeted *versus* TR MRI-targeted biopsies, their effectiveness, and complications.[82] These ongoing and future trials will provide important data on comparative effectiveness and risk profile of TP *versus* TR approach for PBx.

The modern era of TP PBx

While the flaws of TR approach have been known for long, the TP movement has gained steam only in the last few years. Development of effective local anesthesia, assistive technology (i.e. TP access systems, robotic assistance, and imaging), and implications in newer treatments (i.e. focal therapy) has facilitated the dawn of a new era of TP PBx.

Local anesthesia

As alluded to throughout the history of TP PBx, one of the major limiting factors for a TP PBx is the perceived need for general anesthesia. General anesthesia presents with its own risks, scheduling difficulties, and expenses. Local anesthesia for TP biopsies allows for a much more streamlined process for a safer and better diagnostic process. For TR, local anesthesia with a periprostatic nerve block is the gold standard and sufficient for pain control.[83] The increased pain burden with a TP approach is related to additional layers and structures pierced in addition to the prostate, such as bulbocavernosus, levator ani, and deep transverse perineal muscles.[84]

The development of effective local anesthesia techniques has been one of the biggest drivers for adoption of TP approach in office settings. For local anesthesia for TP PBx, the foundation for pain control is a nerve block. Some suggested localized nerve blocks include subcutaneous perineal block, pudendal nerve block, periapical triangle block, or any combination.[84] Studies have demonstrated pain scores comparable with TR and tolerable with either single nerve blocks or combinations of different types of nerve blocks (i.e. pudendal and digital rectally guided TP periprostatic nerve blocks).[70,85–87] An analysis of over 1200 patients by Stefanova *et al.*[19] found skin infiltration followed by periprostatic infiltration results in similar discomfort as TR without any change in complications. Szabo *et al.* reviewed 12,000 cases under local anesthesia and found adequate pain control and minimal complications, with a recommendation that it can be integrated into normal clinic workflow with only local anesthesia providing evidence supporting feasibility of TP performance within clinic settings.

The freehand technique and TP access systems

The free-hand technique for TP biopsy can be performed without acquisition of expensive stepper and brachytherapy grid combination and has been shown to be as effective in cancer detection as the TRUS-TR PBx.[48,88] However, the free-hand technique requires a specific skill set and has a learning curve. Following a single midline or bilateral skin punctures in the perineum, access point(s) are created and can be cannulized with the biopsy device to optimize local anesthesia and pain by limiting needle sticks. Utilizing a cannula, the biopsy needle can pivot and be directed through the prostate.[2,48,89,90] A disadvantage of the free-hand technique is the dissociation of ultrasound probe and sampling needle. This led to the TP Access Systems, such as Precision Point (Perineologic, Cumberland, MD, USA), which comprised a clamp, a needle carriage, and a 15-gauge access needle.[89] The device is secured to the ultrasound probe, which stabilizes the biopsy needle in the correct plane as the linear ultrasound array.[2,71,89] The development of free-hand approach along with the needle guides (such as Precision point and SureFire) has provided freedom from brachytherapy grids previously used to obtain template TP biopsies.

Robotic assistance

The automation of PBx with robot assistance was created to reduce human error associated with

needle placement and appropriate needle trajectory.[2,48] Robot assistance requires a similar cannulization process as that of the free-hand TP technique, with the calculation of needle placement while accounting for patient positioning. The biopsy guide is positioned at the level of the perineal skin and the device then automatically computes trajectories of all targeted cores and/or template cores. The Bio-Xbot system (Biobot Surgical, Singapore, China), piloted in a 2011 study by Ho *et al.*,[91] was used for PBx of 20 men with no significant postoperative complications after a mean of 28.5 core biopsies. Miah *et al.*[92] performed a prospective study of robot-targeted MRI-TRUS fusion TP PBx with the iSR-obot™ Mona Lisa System (Biobot Surgical Ltd, Singapore) and concluded that robot assistance can decrease the number of cores required for PBx, decrease costs, increase efficiency, and create an opportunity for combined PBx and focal ablation therapy of the prostate in the same session. Disadvantages of robot-assisted PBx include significant procedure expense[2,92] and lengthier procedure times.[93] The monetary and time expense challenge patient tolerability and cost, and availability of the operating room. Nonetheless, further research is needed to explore the cost–benefit analysis of robot-assisted PBx.

Conclusion

The modern TP PBx reflects a significant reversion to what was once the gold standard. Dating back nearly one century ago, a TP approach was first utilized to biopsy the prostate with an open perineal PBx persisting as standard for much of the 20th century. Moving forward, the TP approach evolved in efforts to maximize diagnostic accuracy and minimize morbidity. Despite these innovations, TR PBx has persisted as the dominant method since the 1980s due to the convenience and efficacy found with the use of TRUS and sextant sampling. Recently, data have accumulated indicating significant infectious concerns and some diagnostic limitations of a TR approach *versus* a TP approach. Furthermore, major advancements in prostate imaging, development of effective local anesthesia technique, assistive technology (i.e. TP access systems, robotic assistance), and implications in newer treatments (i.e. focal therapy) have made TP PBx more convenient, safe, and efficacious. This significant evolution over the past 100 years has facilitated the modern TP PBx's movement into standard practice that will likely persist for years to come.

Author contribution(s)

Benjamin Schmeusser: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Brandon Levin: Investigation; Writing – original draft; Writing – review & editing.

Daniel Lama: Writing – review & editing.

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Conflict of interest statement

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Availability of data and materials

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