Review Article on Surgery for Urologic Cancers

Transrectal ultrasound biopsy of the prostate: does it still have a role in prostate cancer diagnosis?

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Abstract: Transrectal ultrasound (TRUS) guided biopsy of the prostate has been a standard diagnostic approach for prostate cancer over the past thirty years. Today, the role of TRUS biopsy is being challenged by transperineal (TP) prostate biopsy due to concerns over the safety and diagnostic yield of TRUS biopsy. TRUS biopsy still offers a convenient, reliable and accessible tool for diagnosing prostate cancer in the majority of patients. It continues to play a role in prostate cancer diagnosis, especially where hospital resource allocation is limited, including the public sector. TRUS biopsy has low rates of severe complications, although there remains room for improvement in current practice to improve the tolerability and reduce the incidence of post-biopsy infection.

Keywords: Transrectal ultrasound (TRUS); biopsy; prostate cancer

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Introduction

Transrectal ultrasound (TRUS) guided biopsy of the prostate is performed to obtain a histopathological diagnosis of prostate cancer and has been a mainstay of urological practice for almost thirty years. In that time, the techniques involved have been refined to improve the detection rate of malignancy, to better estimate tumour burden and to assist in surgical planning. Similarly, improvements in peri-operative care have enhanced tolerability and reduced the associated sepsis rates complicating this biopsy technique.

A review of TRUS biopsy is timely as technology advances. An increasing body of evidence has emerged in support of transperineal (TP) biopsy as the preferred technique for pathological sampling of the prostate gland; however, TRUS biopsy remains accessible and widely practiced, and is likely to have a role in urological practice for some time.

This review addresses the history and development of TRUS biopsy, refinements in technique and clinical practice, the advantages and disadvantages of TRUS when compared to TP biopsy, and the evidence surrounding TRUS biopsy in today's practice.

A history of TRUS guided biopsy of the prostate

The first transrectal biopsy of the prostate was described by Astraldi in 1937 (1). The anatomical position of the prostate lends itself to easy palpation and thus superficial biopsy techniques were feasible. TRUS was first applied by Takahashi and Ouchi in 1964, and was further refined by Watanabe and colleagues in 1967 (2). As technology evolved, abnormalities associated with locally advanced prostate adenocarcinoma were soon detectable using TRUS (2).

The first modern TRUS biopsy

In 1989, Hodge and colleagues described the first clinically useful TRUS guided prostate biopsy. This was achieved by aligning palpable abnormalities and sonographic findings to guide biopsy (3). Hodge subsequently described the sextant technique for systematic random biopsy of the prostate. Using a spring-loaded biopsy gun, mapped biopsies were taken from the bilateral prostatic lobes at the apex, middle and base. Hodge proposed that this could be a useful aid in estimating the tumour grade, stage and surgically relevant anatomical location, as compared to targeted biopsy of abnormal prostatic lesions alone (4). It subsequently became the standard diagnostic approach for prostate biopsy.

Refining the technique

As TRUS biopsy entered standard clinical practice, clinicians began to correlate biopsy findings to the overall tumour burden. Dietrick and colleagues proposed that tumour volume could be linked to the size of malignant tissue in the TRUS biopsy core, and that this information could guide cancer management (5). Reliable prediction of tumour volume required improvements to the traditional sextant technique, and the optimal location and number of biopsies was a source of published debate. Variants of this method have been adopted in different centres to improve diagnostic yield. These modifications focused on increasing the number of cores taken while targeting the lateral aspect of the prostate to better sample the peripheral zone (6). Additional lateral biopsies were also employed in larger prostates (7). These variant biopsy techniques improved prostate cancer detection rates by a range of 20–35% (6-9), and have been widely adopted in Urological practice.

TRUS biopsy technique—an example

A standard technique as performed in our institute is described as follows. TRUS biopsy of the prostate is performed as a day case. The patient receives 500 mg of oral ciprofloxacin one hour before the procedure. The urologist is positioned to the right of the supine patient. The patient is then moved into the left lateral decubitus position to commence the procedure.

Digital rectal examination is performed, and findings are recorded. A Bard spring-loaded biopsy gun and a 7 MHz endorectal biplanar ultrasound probe are used. The probe is covered with ultrasound jelly, a thin plastic sheath, and a repeat coat of jelly. The probe is inserted into the rectum and is directed toward the anterior wall, where the prostate can be visualised. Five millilitre of 1% lidocaine is injected into the peri-prostatic neurovascular bundles on each side of the basolateral aspects of the prostate. The prostate volume is then measured, before 14 systematic core prostate biopsies are obtained. Two cores are taken from both sides of the base, mid, and apex of the prostate. Bilateral samples are obtained from the transition zone.

Complications

TRUS biopsy is an overall well tolerated procedure. When surveyed, over 80% of patients who underwent TRUS biopsy in our centre would have a repeat procedure under local anaesthetic as required (10). TRUS biopsy is associated with some risks including pain, acute urinary retention, haematuria, haematospermia, rectal bleeding, erectile dysfunction, infection and sepsis (11). The rising rates of infection and sepsis internationally are of concern and are discussed in more detail below. The relative measure of acute urinary retention post biopsy is also reviewed.

Comparing TRUS biopsy against TP biopsy

The advantages and disadvantages of TRUS biopsy compared to TP prostate biopsy are summarised in *Table 1*, and expanded upon below.

Advantages of TRUS biopsy

Fast, convenient, and familiar

TRUS biopsy is a core urological procedure performed by most practising urologists. TRUS biopsy is easily performed in consulting rooms or a minor procedure suite, and takes approximately ten minutes to complete, including the administration of local anaesthesia (LA). Furthermore, the required equipment is widely available in urological centres.

LA

Surprisingly, TRUS biopsy was initially thought to be well tolerated by patients, and analgesia was not routine in the early 1990s. Evidence subsequently emerged to suggest that TRUS biopsy resulted in discomfort and pain in 65% to 90% of patients (12-14). Nash and colleagues demonstrated that peri-prostatic nerve blockade (PPNB) with lidocaine significantly improved pain scores (14). PPNB at the time of TRUS biopsy has since become standard practice for most

Table 1 Pros and cons of TRUS biopsy *vs.* TP biopsy of the prostate

Item	TRUS	TP biopsy
Pros	Fast	Low risk of urinary sepsis
	Convenient	Template approach—stable, assists in cognitive fusion
	Familiarity	Access to the anterior prostate
	Local anaesthesia	
	Lower risk of urinary retention	
	Cost-effective	
Cons	Antibiotic prophylaxis required due to risk of infection and sepsis	Expensive
	Limitations in targeting	Time-consuming
		Usually under general anaesthesia
		Higher rates of urinary retention

TRUS, transrectal ultrasound; TP, transperineal.

clinicians (15-17).

Several other analgesic modalities have been trialled to improve the comfort of TRUS biopsy. A review by Lee and colleagues in 2014 confirmed that PPNB had the strongest evidence for optimising comfort during TRUS biopsy. Intrarectal local anaesthetic gel was not found to significantly improve pain outcomes. Propofol, benzodiazepines and opioids may decrease the discomfort experienced during TRUS biopsy, but are associated with additional anaesthetic costs, safety, and longer post-biopsy recovery. These analgesic options remove much of the benefit of TRUS biopsy, which is advantageous in low resource, high volume centres. Peri-operative use of rectal diclofenac was not found to significantly decrease patient discomfort (10).

Short-acting Inhaled anaesthetic agents may be of benefit but require further research (18). Inhaled methoxyflurane (Penthrox) may be an effective adjunct to PPNB while performing TRUS biopsy and is currently being investigated in a multi-centre randomised controlled trial (RCT) in collaboration with the Australian and New Zealand Urogenital and Prostate Trials Group (ANZUP). This *Pain-Free TRUS-B Trial* has nearly fully accrued 420 participants (19).

Cost effective and accessible

TRUS biopsy is extremely cost-effective compared to TP biopsy, which requires access to an operating theatre and is usually performed under a general anaesthetic. A brachytherapy grid is frequently used to assist in either cognitive fusion or saturation TP biopsies, and the necessary equipment may be unavailable in many smaller Urology centres. The procedure takes around thirty minutes with extra time required for anaesthesia. TRUS biopsy allows for discharge immediately post-procedure and lends itself to rapid access diagnostic services, whereas TP biopsy requires a day-case admission and increased nursing support. These factors all favour the cost-effectiveness of TRUS biopsy in the public hospital or resource limited healthcare setting.

The economic benefits of TRUS are particularly relevant in the authors' institution. In rural Western Australia, patients travel up to 3,000 km to access subspecialty care. For these patients, a rapid access approach provides multiparametric MRI (mpMRI) and TRUS biopsy in one day to facilitate fast, cost-effective allocation of healthcare services and rapid cancer diagnosis (20). Patients are able to return home quickly, minimising hospital stay, transport and accommodation costs.

Lower risk of acute urinary retention

TRUS biopsy has been associated with post-procedural urinary retention, requiring insertion of an indwelling catheter until inflammatory changes resolve. The risk of retention is generally regarded as lower for TRUS than TP biopsy. In a 2017 meta-analysis, Borghesi and colleagues suggested that urinary retention occurs in 0.4–6% of patients who undergo TRUS biopsy. In comparison, 1.7–11.1% of patients who received TP biopsy developed

urinary retention (21). Included in this dataset was a cohort study of 3,000 patients by Pepe and colleagues, who demonstrated that the risk of urinary retention post-TP biopsy significantly rose as the number of biopsy cores increased (22).

Tamsulosin has been trialled to minimise the risk of acute urinary retention. Chung and colleagues randomised 88 patients who did not take any previous pharmacotherapy for lower urinary tract symptoms, of which half received tamsulosin from one day pre-TRUS biopsy until seven days post. There was a significant improvement in flow rate, post-void residual, and retention in the tamsulosin group (23). Despite the small numbers in this study, there may be some benefit to the use of alpha-blockers in the peri-biopsy period.

Disadvantages of TRUS biopsy

Post-TRUS biopsy infection and sepsis

The most significant complication of TRUS biopsy is sepsis, which in 2016 was re-defined as "life threatening organ dysfunction caused by a dysregulated host response to infection" (24). Historically, it was defined as "infection plus systemic inflammatory response syndrome" (25,26). The risk of post-operative infection is not surprising, as the TRUS biopsy needle must pass through the rectal wall to access the prostate, inoculating rectal flora. The empirical antibiotic choice at TRUS biopsy is ciprofloxacin. Multiple studies have been performed to reduce the risk of infective complications, to reduce the rectal flora and to treat drug-resistant bacteria.

Historically, infection complicated approximately 1% of patients who underwent TRUS biopsy, but this figure has risen to between 2–4% in recent years (27,28). The increasing infection rates may be secondary to fluoroquinolone resistance, attributed to recent infection and antibiotic use (28,29). Up to one-quarter of men undergoing prostate biopsy may be colonised with fluoroquinolone-resistant rectal flora (30). Men with significant risk factors for sepsis such as immunocompromise, type 2 diabetes mellitus, recent hospitalisation and COPD (28), could be considered for TP rather than TRUS biopsy.

The duration of pre-biopsy fluoroquinolone prophylaxis appears unrelated to infection risk. Bangash and colleagues performed a prospective analysis of post-biopsy infection rates in 2018, and suggested that a single dose of ciprofloxacin 500 mg was non-inferior to a three-day course of twice daily ciprofloxacin in over 700 patients (31).

Rectal disinfection

Rectal disinfection has been trialled in an attempt to reduce the risk of TRUS biopsy related sepsis. In 2014, Pu and colleagues performed a meta-analysis of povidone-iodine preparation with antibiotic prophylaxis, and declared that this significantly reduced the rate of post-biopsy infective complications compared to antibiotics alone (32). However, no adequately powered RCT has confirmed this suggestion. This technique does not remove the need for antibiotic prophylaxis.

Targeted antibiotic prophylaxis

There may be a clinical role for pre-biopsy rectal swabs and targeted antibiotic prophylaxis. In a 2014 meta-analysis, Roberts and colleagues declared that fluoroquinolone resistant swabs were significantly more likely in patients who had previous exposure to these antibiotics. Infection rates post-TRUS biopsy were significantly higher in people who received pre-operative empirical fluoroquinolones (3.3%) as compared to targeted antibiotic prophylaxis (0.3%) based on rectal flora results (33), although it is possible that many of these patients with fluoroquinolone-resistance rectal isolates were given carbapenems (discussed in more detail below). In a systematic review of nine cohort studies and over 4,500 patients, Cussans and colleagues identified that targeted antibiotic prophylaxis decreased the rate of infective complications from 4.55% to 0.72%, and sepsis from 2.21% to 0.48% (34).

Carbapenem prophylaxis

The use of carbapenem prophylaxis appears to decrease the rate of infective complications following TRUS biopsy in populations with known fluoroquinolone resistance. In New Zealand, Losco and colleagues performed a prospective audit of ertapenem use in patients deemed to be at high risk of TRUS-related sepsis. These patients had received fluoroquinolones in the 12 months prior, or travelled to South-East Asia within the past 6 months, or were immunocompromised (including diabetes). In 80 high-risk patients who received ertapenem, there were no cases of sepsis compared to a rate of 6.7% within the cohort who received ciprofloxacin and amoxicillin-clavulanate (35). In several Australian studies, carbapenem use has been associated with a zero-sepsis rate (31,36). Despite the apparent reduction in TRUS biopsy related infection, the use of carbapenems should be minimised where possible

due to the threat of Enterobacteriaceae carbapenem-resistance. This is a major global health concern as it is difficult to treat and is associated with a high-mortality (37). Therefore, carbapenems cannot be recommended for routine prophylaxis.

Diagnostic yield and access to the anterior prostate

There is a lack of high-quality data comparing the diagnostic yield of TRUS biopsy against TP biopsy. A 2017 meta-analysis from Xue and colleagues reviewed 13 studies comprising over 4,200 patients, and concluded that the overall prostate cancer detection rate between TRUS and TP biopsy was not significantly different (38). No RCT supporting an overall benefit of TP over TRUS biopsy exists. Although mpMRI and fusion technology are suspected to improve sensitivity in small and anterior lesions, further adequately-powered studies are required (39).

Although tumours in the anterior zone are less common than in the peripheral zone, the relative inaccessibility of anterior zone sampling is a clear disadvantage of TRUS compared to TP biopsy. In men with suspicious PSA findings and benign histopathology on TRUS biopsy, TP biopsy should be considered to assess the anterior zone (40). In centres with both TRUS and TP biopsy, patients with suspicious anterior zone lesions on mpMRI should be allocated to a TP biopsy where possible.

mpMRI prostate and targeted biopsy

The use of pre-biopsy mpMRI may aid in the detection of clinically significant prostate cancer (41). The PRECISION study randomised men to undergo either systematic or targeted biopsies and suggested that targeted biopsy was more sensitive for the detection of clinically significant prostate cancer (42). MRI-FIRST studied 251 men who received mpMRI followed by both targeted and systematic TRUS biopsies. The rate of clinically significant prostate cancer was higher when both targeted and systematic biopsies were performed, and each technique would have missed lesions if performed alone (43). Systematic biopsy ensures the thorough diagnostic assessment of the prostate allowing for the limitations of mpMRI and cognitive fusion using TRUS.

Although mpMRI is typically reliable for identifying higher-grade (ISUP Grade >2) tumours (41), it does have limitations. Up to 16% of clinically significant lesions can be missed, resulting in a false negative diagnosis (44). Therefore, a decision to abandon biopsy based on negative mpMRI results should be limited to high-volume uro-radiological units with extensive operator experience. A significant proportion of the tumours missed on mpMRI will be in the peripheral zone, which is well sampled by TRUS biopsy. Many healthcare systems do not have the resources required to provide routine pre-biopsy mpMRI or fusion software for targeting lesions, thus maintaining the relevance of TRUS biopsy.

Conclusions

TRUS-guided prostate biopsy has been the standard diagnostic approach for prostate cancer for nearly 30 years and remains a rapid, cost-effective and generally well tolerated technique. TRUS biopsy does have disadvantages, the most significant being the risk of infective complications. With the careful selection of patients and sensible antibiotic use however, these complications can be minimised.

In many cases, such as in patients with risk factors for sepsis and with anterior prostate lesions, TP biopsy should be used in preference to TRUS. However, TRUS biopsy will likely remain a valuable tool in low resource and high-volume centres for some time.

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Footnote

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