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Prostate Cancer Diagnosis: Biopsy Approaches

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Abstract: Prostate cancer is a common and increasing malignancy in men. Tissue is generally obtained using prostate biopsy for diagnosis and risk stratification. There are many prostate biopsy techniques. Historically, the transrectal approach has been the most adopted. In many centers, however, there has a been a shift towards transperineal prostate biopsies, increasingly performed under local anesthetic. The transperineal approach has proven advantages, including better sampling of the anterior area of the prostate and lower infection rates. Biopsies are typically performed using a combination of a systematic and targeted approach. Targeting of lesions identified by magnetic resonance imaging can be performed cognitively, assisted by a fused imaging approach with the transrectal ultrasound, or directly within the magnetic resonance imaging scanner. There are several novel developments in the field, which include robotic techniques to guide biopsy needles based on fusion images or directly targeting lesions robotically during in-bore magnetic resonance imaging.

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INTRODUCTION

Prostate cancer is common. In 2020, it was the second most frequent malignancy in men worldwide. The highest incidence is found in Northern and Western Europe, the Caribbean, and Australasia; the lowest is in Asia and Northern Africa (1). Non modifiable risk factors include advancing age, ethnicity, and family history with a link to the BRCA gene mutation (1, 2). Numerous modifiable risk factors have also been identified and include smoking, levels of physical activity, metabolic syndrome, and sexual activity/ejaculatory frequency (1–5). Various dietary factors have been attributed to prostate cancer development and include well-done meat, sugar-sweetened beverages, dairy products, and processed foods (1, 2, 6–8).

Prostate cancer is often initially detected opportunistically by blood tests examining levels of prostate specific antigen (PSA) or by digital rectal examination (DRE). The latter examination relies on user experience and has been found to have a low sensitivity of around 50% in a primary care setting (9). PSA is a protease secreted by the prostate gland that has been utilized as a biomarker for prostate cancer since the late 1980s (10). It is not only useful in diagnosis but also for risk stratification and, following treatment, as a marker of recurrence (11). Widespread screening for prostate cancer using PSA, however, is a contentious issue. Evidence suggests that PSA screening can identify additional cancers; however the majority are low grade with no improvement seen in overall survival as a result (12). As such, international guidance focuses on individualized risk and shared decision making with risk-benefit discussion so that patients are informed of the potential for false positives and over-investigation/treatment before undertaking a PSA test (11, 13, 14).

Where there is suspicion of localized prostate cancer, such as abnormal DRE or raised PSA, further investigation is usually with multiparametric magnetic resonance imaging (mpMRI) of the prostate (11, 15, 16). mpMRI should be reported using the Likert or Prostate Imaging-Reporting and Data System (PI-RADS) scoring systems which standardize interpretation. Both systems score the investigation on a scale of 1 to 5 whereby 1 suggests that clinically significant disease is highly unlikely to be present and 5 suggests it is highly likely to be present (17, 18).

Biopsies are usually performed for abnormal DRE or mpMRI result suggestive of clinically significant disease, though the decision for biopsy should always be made in clinical context and in discussion with the patient. The use of prostate cancer risk calculators can assist decision making and are advocated by guidelines (11, 15). Prostate biopsies aim to confirm the diagnosis and assess the histological architecture using the Gleason grade, which is used to create a Gleason score, or more recently ISUP grade (19, 20). The Gleason score or ISUP grade is then used alongside mpMRI staging and PSA to stratify locally advanced prostate cancer risk. Risk groups vary depending on the guideline typically utilizing a 3-tier

system of low, intermediate, and high risk (11, 21). In the United Kingdom (UK) however the National Institute for Health and Care Excellence (NICE) have recently adopted the Cambridge Prognostic Criteria (CPG) which is a 5-tier system (22). There is evidence that suggests that the CPG system may allow for more accurate prognostication and therefore more specific and appropriate treatment (22, 23). Once risk-stratified, patients can then be counselled on treatment options appropriate for their prostate cancer, with active surveillance usually offered to the lower risk groups and radical treatment for those at higher risk (11, 21, 22). This underlines the importance of accurate histological information obtained from biopsy.

PROSTATE BIOPSY PRINCIPLES

Prostate biopsy was originally performed by targeting abnormalities felt on DRE with a biopsy needle (24). Whilst biopsy is still commonly undertaken by a transrectal (TR) approach, the methodology and improvements in targeting abnormalities have improved considerably. Furthermore, there has been a shift toward a transperineal approach. The practicality and merits of different approaches and techniques are discussed herein.

Prostate anatomy

Anatomically, the prostate is divided into glandular zones—comprising of peripheral, central and transitional zones—and non-glandular anterior fibromuscular zone, all of which are contained within the prostatic capsule (Figure 1) (25). Additionally, the peri-urethral zone is a thin layer of tissue around the urethra consisting of small ducts which can give rise to the median lobe in benign prostate hypertrophy (BPH) (26).

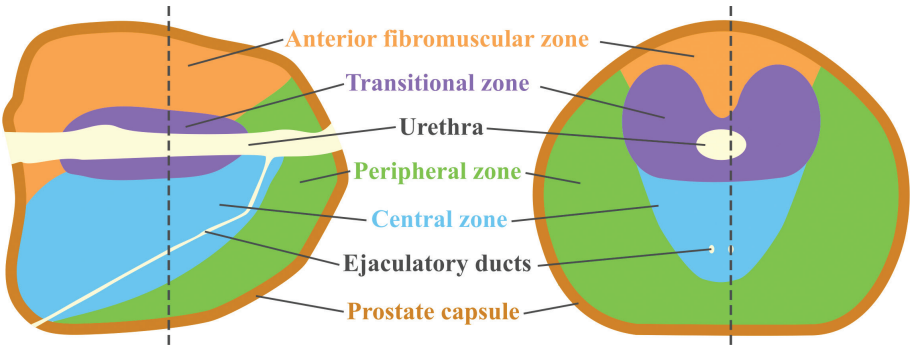

Figure 1. Zonal anatomy of the prostate. Parasagittal (left) and transverse (right) sections of the prostate, where dotted lines represent their intersection. The diagram illustrates the zonal anatomy, anterior fibromuscular zone in orange, peripheral zone in green, transitional zone in purple and central zone in blue.

Transrectal ultrasound

As a diagnostic modality, transrectal ultrasound (TRUS) has been found to have a low accuracy for detecting prostate cancer (27, 28). As a result, TRUS is primarily used to visualize and guide biopsy needles during the procedure (29).

Procedural analgesia

Prostate biopsy is recognized to be an uncomfortable procedure. Pain caused by TR biopsy is multifactorial, initially arising from the insertion of the probe, followed by piercing of the rectal mucosa and prostatic capsule (30). Insertion of the probe stimulates rectal stretch receptors, and some evidence suggests that those with a low anorectal compliance find biopsies more uncomfortable (31). Rectal mucosa is considered to be insensate proximal to the dentate line, however, apical biopsies may traverse this boundary due to the acute angle required and are considered among the most painful location to biopsy by the TR approach (30, 32). Prostatic innervation is predominately from within the capsule, pain appears to increase with the number cores taken with a cumulative effect, increasing after each consecutive biopsy (30, 33, 34). It has also been observed that younger patients report a higher rate of discomfort (31, 35, 36).

Analgesia is therefore an important component of the procedure, as whilst many men are able to tolerate the procedure without, in those who find it particularly uncomfortable it can limit the procedure and lead to refusal of re-biopsies, if required (32, 37, 38). Periprostatic nerve blockage (PNB) has been found to be an effective method of reducing pain during the procedure (39, 40). The extra injections required for a PNB do not appear to confer additional risk, including that of infection, although operators need to be mindful of local anesthetic (LA) toxicity which can occur if it is injected directly into the prostatic venous plexus (39–42). PNB is performed using a spinal needle under ultrasound guidance, 1% lidocaine is typically the agent of choice and between 5–10 ml of this is utilized, with evidence suggesting 10 ml to be an optimal dose (43). There are a multitude of approaches, the most common is the basal block whereby LA is infiltrated in the space between the seminal vesicle and prostate on either side, this area is identifiable as a hyperechoic pyramid on ultrasound termed “Mount Everest” sign (44, 45). Apical blocks have also been described alone or in combination with the basal technique, though there is conflicting evidence with some studies concluding equivocal efficacy and others suggesting apical approach may be superior (43, 46–50). Discomfort caused by probe insertion is not ameliorated by PNB and is part of the procedure that some men find the most uncomfortable (49). Additional topical anesthetic, usually in the form of intrarectal lidocaine gel, is therefore commonly used in combination with PNB and can safely reduce pain associated with probe insertion (39, 40). A less commonly used alternative to intrarectal lidocaine is topical glyceryl trinitrate (GTN) which has also been shown to be effective (51, 52).

Transperineal (TP) biopsies were initially performed under a general anesthetic (GA) but increasingly are undertaken as a LA procedure. In these cases, LA is infiltrated into the perineal skin prior to a PNB performed as described above but via the perineum (53, 54).

Equipment

An endorectal ultrasound transducer with a frequency in the range of 6–12 MHz is commonly used. Ideally, transducers should be biplane, allowing visualization of transverse and longitudinal sections simultaneously (55). When utilizing the probe for TR biopsies, two main types exist: (i) end-firing with a biopsy needle which runs parallel to the probe with a curved transducer at the tip allowing for biopsies to be taken in the sagittal or transverse plane (56, 57); and (ii) side-firing probes wherein the biopsy needle traverses the probe and a longitudinal transducer allows for biopsies to be visualized in the sagittal plane (56, 57). Initially retrospective studies suggested better prostate cancer detection with the end-firing probe because of its ability to sample apical and lateral regions of the prostate; however, subsequent randomized control trials have shown no difference between the techniques (56, 58–61).

Biopsies were originally performed using hand-driven needles but have universally shifted to the use of a spring-loaded biopsy needle gun due to gun-driven biopsies providing better tissue yields (62, 63). There are multiple biopsy guns available on the market, the majority utilize 18-gauge needles that are between 20–25 cm long. The mechanism consists of a double trocar where an inner trocar is fired into tissue, followed by an outer trocar around this to cut the tissue core; the outer trocar then retracts and the tissue can be retrieved via the tissue tray, a windowed aspect of the inner trocar (64).

Depending on the ultrasound machine, markers are typically superimposed onto the image at 5 mm intervals to allow estimate of where the gun will fire, the needle typically fires 25 mm into tissue with the windowed aspect present in the middle 15 mm. It was initially reported that tissue obtained in the first 5mm would not be contained within the biopsy and that position should be adjusted as such; however, this has subsequently been shown not to be the case (64, 65).

Biopsy core length improves quality of tissue and sensitivity for diagnosis with suggestion that 12 mm is the minimum length required, whereas needle diameter does not appear to improve prostate cancer detection rates (66–71). Most biopsy guns are designed to obtain standard core lengths of 20 mm, some devices have been designed to take longer cores, though longer needles have an increased risk of deflection and therefore potentially lower sampling accuracy (72, 73).

Procedure

Transrectal biopsies are typically performed in the left lateral decubitus position with knees and hips flexed to approximately 90 degrees. Transperineal biopsies are most commonly performed in the lithotomy position, though the left lateral decubitus position has been described (74). A DRE is carried out prior to assess the prostate and correlate with ultrasound. Palpable abnormalities should be considered for targeting at biopsy. The probe is introduced with lubricant and analgesia administered as discussed. Prostate size, specifically volume, can be estimated using the ellipsoid volume formula which can be used to calculate the PSA density, or in patients with benign prostatic hypertrophy, can be used for treatment planning. Biopsies can then be taken in either a systematic or targeted approach. The transrectal and transperineal biopsy techniques are shown in Figure 2.

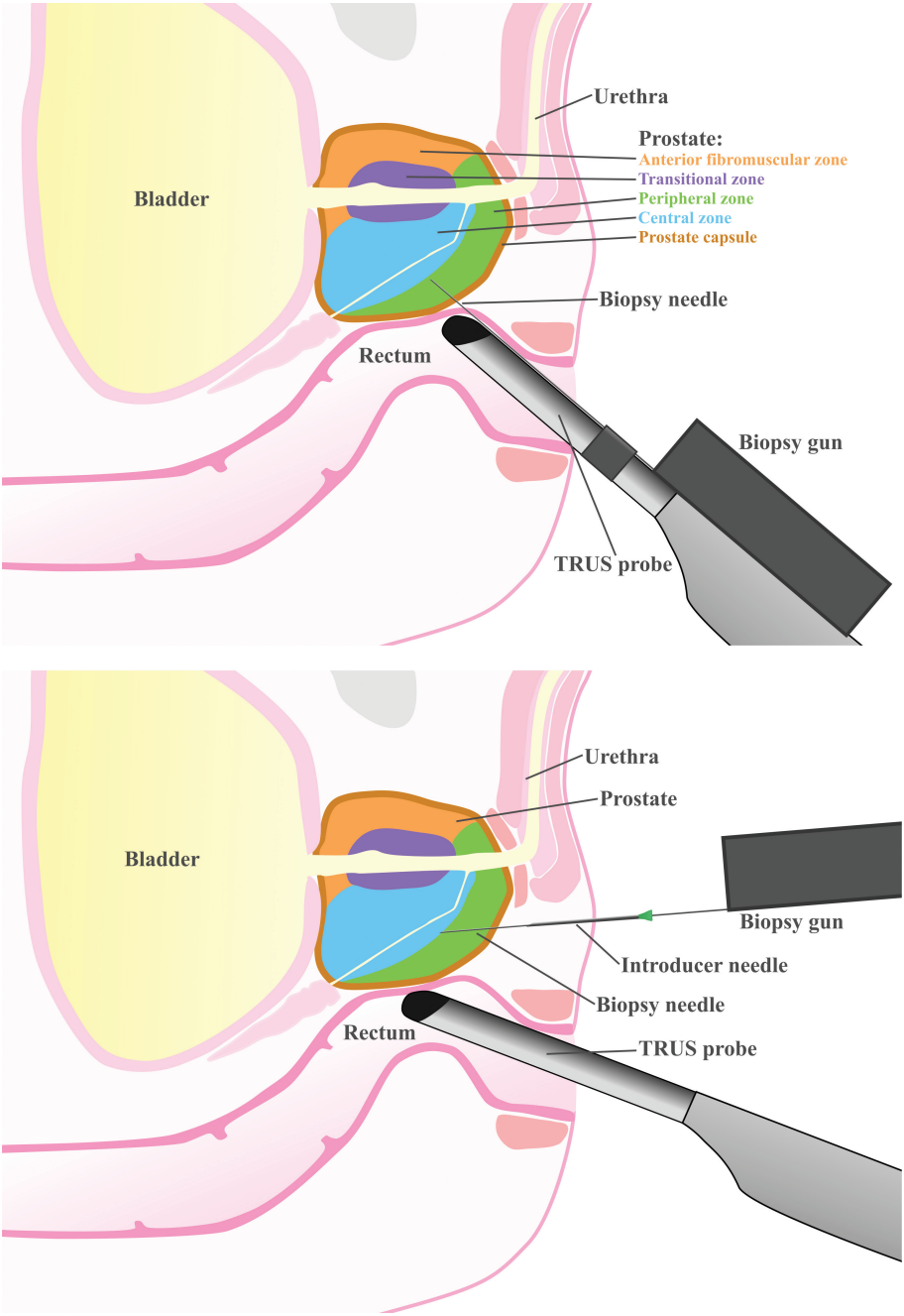

Figure 2. Parasagittal view of a prostate biopsy. Top, Transrectal approach using an end-firing probe. Bottom, Transperineal approach using the double freehand technique.

One aspect this illustrates is the difficulty of sampling the anterior prostate by the transrectal approach, an area which is more readily accessed by TP biopsy (75, 76).

SYSTEMATIC BIOPSIES

There are several systematic biopsy protocols. Initially, when transrectal prostate biopsy was developed, it was using a sextant pattern, with 3 cores taken from each side of the prostate, and was found to be superior to targeting lesions identified using TRUS (29). However, the sextant protocol has been found to have a high false negative rate, particularly missing apical and lateral lesions (77–79).

Transrectal extended systematic biopsy

Several alternative biopsy protocols have been examined with studies suggesting sensitivity can be increased by increasing the number of biopsy cores taken (29, 77–80). Further evidence, including a large systematic review, has suggested that 10–12 cores seem to be an optimal number, in what is termed an extended biopsy, and which has now become the standard of care (11, 81–83). The extended biopsy utilizes the traditional sextant biopsy with additional cores taken from the more lateral aspects of the prostate which has been shown to increase diagnostic yield (77, 84). The number of cores taken should be adjusted based on the size of the prostate with smaller prostates requiring fewer cores (84). An example of core sampling locations is shown in Figure 3.

Transrectal saturation biopsy

Transrectal saturation biopsy was developed in response to patients with a high clinical suspicion of prostate cancer who had undergone multiple negative biopsies;

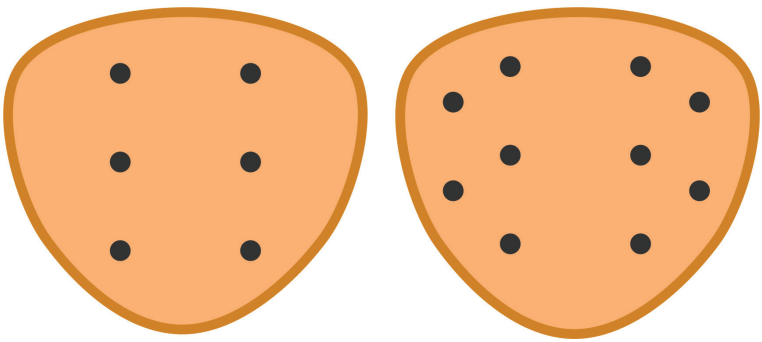

Figure 3. Prostate biopsy schemes. Examples of sextant (left) and extended ten core (right) prostatic biopsy schemes as seen in the coronal plane, from the perspective of a TRUS biopsy.

it involves taking a much higher number of cores, usually between 20–30 (85). In the original 2001 paper, a detection rate of 34% was found amongst men who on average had undergone two previous negative sextant biopsies (85). Following its development, standard practice has now changed with patients undergoing extended biopsy protocols plus targeted biopsies in most cases. However, the role for saturation biopsy remains for those patients with negative biopsy and high clinical suspicion; this is typically in the context of persistently high PSA or abnormal mpMRI.

Transperineal template mapping biopsy

Transperineal biopsies initially were developed using the grid and stepper technique to perform a systematic saturation biopsy of the prostate under general anesthetic. This technique utilizes the brachytherapy needle guide developed for insertion of radioactive seeds and consists of a grid punctuated with holes to pass a needle spaced 5mm apart. If sampling the whole gland, this can result in 50–70 cores being taken. This method is highly sensitive, missing only 5% of small prostatic lesions compared with 30–40% missed at TRUS biopsy (86).

Transperineal biopsy schemes

To reduce the number of cores taken, various biopsy schemes utilizing the grid and stepper exist. The Ginsberg scheme was defined in 2013 to standardize this (87). The number of cores sampled is dependent on prostatic size but broadly splits the prostate into three sectors on each side, anterior, mid, and posterior, with four cores taken from each, and additional cores from a basal sector used in large prostates totaling 24 or 32 cores respectively (87). The Ginsburg scheme has been shown to yield high rates of cancer detection and is illustrated in Figure 4 (88). Whilst some studies report grid biopsies performed under local anesthetic, due to

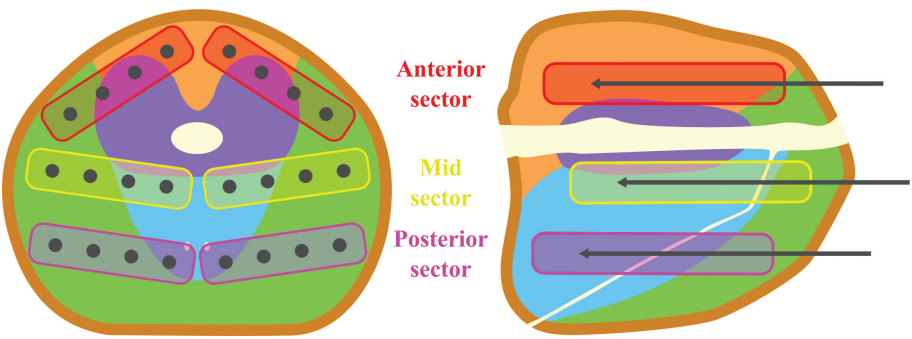

Figure 4. Schematic demonstrating the Ginsburg protocol for a small prostate (<30 cc) in parasagittal and axial views. Sampling locations are shown across three sectors with four cores taken from each bilaterally, totalling 24 cores. Prostatic zones are as previously labelled in Figure 1: anterior fibromuscular zone in orange, peripheral zone in green, transitional zone in purple and central zone in blue. Adapted from the description of the Ginsburg Protocol by Kuru et al. (87).

the large number of needle punctures via the perineum and a wide spread of local anesthetic that is required, this technique is generally performed under general or regional anesthesia (89, 90). To better facilitate transperineal biopsies under a local anesthetic, alternative techniques have been described.

Transperineal freehand technique

These include the freehand technique whereby a single puncture with an introducer needle is made on either side of the perineum and the biopsy needle passed through, thereby removing the need for multiple skin punctures and allows for local anesthetic to be localized to the limited points of puncture. Typically, local anesthetic is infiltrated in the skin with a 23- or 25-gauge needle, following which a finer spinal needle can be used to infiltrate the subcutaneous tissue, muscular diaphragm and space around the prostate apex as described earlier (91). The number of cores taken using this technique vary with some authors obtaining a smaller number of cores similar to a transrectal biopsy and others following the Ginsberg protocol (53, 91–93). Similar rates of cancer detection have been seen when comparing 10 core transperineal and transrectal biopsy and a systematic review has confirmed similar diagnosis rates between the transrectal and transperineal approach (90, 94). Tolerability of this technique appears to be good with one large series of patients reporting visual analogue pain scores (VAS) of up to 3.1/10 with the most painful aspect often reported as the infiltration of local anesthetic (53). Other series report similar results with average VAS scores between 1–5 (90, 93, 95–97). With one reporting only one of 181 patients abandoning the procedure due to discomfort (96). Advantages of the freehand technique include the reduction of urinary retention rates when compared to the grid technique. In one study, this was 10% for those undergoing grid biopsies and 1% for freehand, despite a similar number of cores being taken (31 vs 28) (91).

TARGETED PROSTATE BIOPSIES

Whilst systematic biopsies are useful at sampling the prostate, targeting abnormal lesions directly, previously practiced in conjunction with abnormal DRE or TRUS images, has become more relevant with the increasing use of mpMRI.

Ultrasound targeted

Hypoechoic lesions on TRUS can often represent prostate cancer and evidence suggests that hypoechoic lesions seen during systematic biopsy are predictors for clinically significant prostate cancer (98–101). However, whether routinely targeting these lesions increases diagnostic yield is less conclusive with conflicting results. One prospective study found no higher detection rate in hypoechoic lesions compared with isoechoic areas whereas another found that 9% of cancers were only present in the cores from hypoechoic lesions and would have been missed by systematic biopsy alone (102, 103). Further studies have reported more modest results with around 3–4% of additional cancers detected solely on cores targeting hypoechoic lesions (104, 105).

MRI targeted

For those patients who have a mpMRI suspicious for cancer, there is strong evidence that there is improved cancer detection if abnormal lesions identified on mpMRI are targeted at biopsy, and reduced diagnoses of clinically insignificant cancers if systematic biopsies are omitted (106–111). Though mpMRI targeted biopsies have been shown to be non-inferior to systematic biopsies, individual studies have shown that mpMRI targeted biopsies alone miss a small proportion, 4–16%, of clinically significant cancers that would be picked up with additional systematic biopsies (112–118). Current guidance is to offer combined systematic and targeted biopsies (11). There is no standard number of cores recommended from each target but a systematic review analyzing diagnostic yield per number of cores taken from mpMRI-targeted biopsies showed incremental gains with each additional core taken, but this benefit became minor after three cores (119). It is generally accepted that in patients who have a negative mpMRI but retain a strong clinical suspicion for prostate cancer, a systematic biopsy should be undertaken (11). This is because whilst mpMRI has a sensitivity for clinically significant prostate cancer of greater than 90%, a small proportion of lesions are not visible; furthermore, mpMRI has been shown to have a lower negative predictive value for those with high PSA (120, 121). Note that a threshold for clinically significant prostate cancer is not clearly defined with a variety of thresholds throughout the literature, though the definition most often used within studies tends to be a Gleason score ≥ 7 (22).

Cognitive targeting

mpMRI-targeted biopsies can be performed in several ways, the most straightforward is cognitive targeting (also known as cognitive fusion or visual estimation) whereby the operator uses the MRI images/report to help direct biopsies at a suspicious area. In this method, the biopsy is conducted by targeting areas on the TRUS images that would correspond to the area on the MRI and can be performed using either the transrectal or transperineal approach. Cognitive targeting using the transperineal approach can be done using a 'double freehand' technique whereby the introducer needle placed in the perineum is separate from the TRUS probe. This is practically more difficult as it requires the operator to manually align the TRUS probe with the needle to keep it in view. To make this technique more user friendly, a selection of devices to assist the process have been introduced. These devices incorporate a guide attached to the probe to keep the needle in line, and hence in view, to enable easier targeting.

Transrectal ultrasound-mpMRI (TRUS-MR) fusion biopsies

TRUS-MR fusion biopsies involve specialized software to overlay areas of interest seen on mpMRI onto TRUS images in real-time so that they can be readily targeted. Two main methods for registering mpMRI images onto TRUS exist; rigid registration whereby images are simply overlayed, or elastic registration which uses software to manipulate the overlaid MRI images to take into account deformation of prostatic anatomy caused by the manipulation of the rectal ultrasound probe.

Whilst some evidence suggests elastic registration is more accurate, the majority of clinical studies show no difference between the two modalities, with operator experience playing a key role in accuracy regardless of technique (122–124). Certainly, inter-operator variability and expertise is a factor, particularly for cognitive and fusion biopsy where a learning curve with higher detection rates of clinically significant prostate cancer associated with experience has been demonstrated (125–127). TRUS-MR fusion biopsies can be undertaken via the transrectal or transperineal approach though evidence suggests that the transperineal approach is better at detecting clinically significant cancers and anterior tumors with a lower rate of complications compared with transrectal (76, 128, 129).

In-bore magnetic resonance image-guided biopsies

In-bore MRI-guided biopsy, whereby MRI is used to guide the biopsy needle directly, avoids some of these difficulties (130). For transrectal in-bore MRI-guided biopsies, patients undergo a diagnostic prostate mpMRI and then return for a guided biopsy. This is usually performed prone using a needle guide which is adjusted and re-imaged until correctly positioned, at which point the biopsy needle is inserted, re-imaged and then biopsy taken (130). MRI compatibility is a key consideration, meaning devices need to be free of ferromagnetic/electronic materials that could interfere with image capture. Whilst the majority of systems use a transrectal approach, transperineal and transgluteal techniques have been described (131, 132).

Evidence to support targeting methodology

The three MRI targeting techniques described above were compared in the FUTURE trial in men with previous negative systematic biopsy and PIRADS 3 or greater lesion on mpMRI, and no difference in detection rates was found between methods, though it was underpowered (133). Some evidence suggests improved detection of clinically significant prostate cancer and reduced detection of insignificant prostate cancer utilizing in-bore MRI compared with TRUS-MR Fusion (134). However, systematic reviews have shown none of the three above methods to be superior, though one did show a trend in favor of MRI-ultrasound fusion over cognitive targeting, at present there remains no clear consensus (135–137). Of note, there appears to be no additional complications seen in utilizing the fusion or in bore approach (138, 139). From a cost and logistics perspective performing in-bore MRI targeted biopsies is clearly a more costly and resource intensive procedure, requiring an MRI scanner, expertise, and compatible equipment. Cost effective analyses have shown cost of in-bore MRI biopsy is similar to general anesthesia transperineal biopsy but more than double that of a local anesthetic transrectal biopsy (140).

Robotic biopsies: TRUS-MR fusion-guided robotic biopsy

Robotic biopsy methods have been developed using TRUS-MR fusion. Various designs exist, though the general principle is that lesions identified on mpMRI and fused with TRUS images are targeted with the robotic arm which defines

penetration angle and depth by positioning a needle guide with stop bar (141–143). The insertion and firing of the needle gun are then performed by the surgeon at the predefined position and depth (142, 143). Though robotic fusion biopsy has been described by both a transrectal and transperineal approach, the majority utilize the latter. One advantage of this is that the system maps out the intended biopsies and correlates an appropriate pivot point to site the trocar needle thereby minimizing the need for repeated skin puncture (142, 143). Whilst the system can accurately target MRI lesions using fusion technology it can also be used to take systematic biopsies with initial studies still showing benefit of taking both targeted and systematic biopsies by this approach (142–145). Though the majority of these early studies utilize general anesthesia, there have been reports of its initial use under local anesthesia with sedation (146). To date, there is limited evidence for fusion robotic biopsy, though one retrospective study reported higher rates of detection for clinically significant cancers and lower complications with transperineal robotic biopsy compared with transperineal cognitive biopsies (147). Robotic guidance likely represents a method to reduce learning curve and standardize biopsies (147).

Robotic biopsies: MRI-guided robotic biopsy

Transrectal in-bore MRI robotic biopsies are performed similarly to standard in-bore MRI biopsy with patients in a prone position within the scanner. A rectal needle guide is inserted and attached to the robotic manipulator which sits between the patients' legs (148–151). The MRI is performed, and area of interest identified, following which the robotic transrectal needle guide is positioned using specialized software with the ability to fine tune the position of the needle path in line with the area to be biopsied (148–151). The robotic arm is MRI compatible by virtue of pneumatic stepper motors powered by compressed air from outside the MRI room (148–151). Once the needle guide is accurately positioned, the patient is removed from the bore of the machine and an MRI compatible transrectal biopsy gun is used within the guide to take a biopsy from the predetermined location (148–151). The advantage of this over the non-robotic method is the speed and ease of needle positioning which otherwise has to be performed manually with the patient removed from the scanner each time. Though there is limited evidence available on this technique at present, early reports suggest a high rate of success and cancer detection (148–151).

PROCEDURAL COMPLICATIONS

Despite being similar procedures, the complication profile of transrectal and transperineal biopsies varies, in particular with respect to the risk of infectious complications.

Infection in transrectal biopsies

For the transrectal approach, infection is a greater consideration due to the passage of the needle through rectal mucosa. Rates of post biopsy sepsis/severe infection

resulting in hospitalization have been reported in around 3% of patients, though up to 10% in one Norwegian series (152–157). Those most at risk of infectious complications include those with pre-biopsy bacteriuria, urethral catheterization, and prior urogenital infection (158). Multiple comorbidities, particularly diabetes mellitus, have been found to be associated with an increased risk of hospitalization (158). Of note, neither increased number of biopsy cores nor the use of a periprostatic nerve block appear to have any bearing on the rate of infectious complications (41).

Antibiotic prophylaxis in transrectal biopsy

A Cochrane review in 2011 concluded that antibiotic prophylaxis is effective at reducing infectious complications in TR biopsies (159). Subsequent evidence has confirmed that antibiotic prophylaxis is more effective if a minimum of 1 day duration is given and commenced at least 24 hours prior to biopsy (160, 161). A cause for concern is the observation of increased fluoroquinolone resistance in some centers, with a baseline prevalence estimated in a meta-analysis from 2012 of around 17% (152, 162, 163). Fluoroquinolone resistance has been found at higher rates in men who have undergone previous fluoroquinolone prophylaxis, those who have undertaken international travel, particularly to areas with increased resistance and those who have had recent hospital admission (158, 162). It has also been observed at higher rates in physicians and relatives of hospital employees (158, 162). Men with fluoroquinolone resistance have been shown to be at higher risk of infectious complications (162, 164). The significance of this appears to be an increase in infectious complications and resultant hospital admissions reported across multiple centers, with one large population study in Canada showing a rise in infection related admissions from 1% to 4% in 10 years (152, 163, 165, 166).

One approach used to combat this has been routine pre-biopsy swabs to determine if a patient has fluoroquinolone resistance, with prophylaxis tailored accordingly. Evidence has shown that this targeted prophylaxis approach reduces overall infectious complications, though rates of sepsis in some studies were found to be unchanged (161, 167, 168). Augmented prophylaxis is another approach, whereby multiple antibiotic agents are used in combination. This has been shown to reduce infectious complications compared to single agent prophylaxis with the majority of studies included within the metanalysis using fluoroquinolone as one of the agents, often in conjunction with an aminoglycoside (161). Recently, there has been concern with regards to increasing recognized adverse effects of fluoroquinolone antibiotics and their use in perioperative prophylaxis has been restricted in some regions (169, 170). As a result, there has been an increased emphasis on alternative antibiotics for prophylaxis. Fosfomycin has been found to be an effective prophylaxis with low rates of resistance and less infectious complications than fluoroquinolones (161, 171–173). Aminoglycoside, piperacillin/tazobactam, and cephalosporin prophylaxis has also found to be comparable to fluoroquinolones (159, 161, 174). Whereas co-amoxiclav has been shown to be less effective (175, 176). Single doses of pre-biopsy carbapenem antibiotics have also been used with good effect and some evidence suggests its use may not select for carbapenem resistant organism (177–180).

Non-antibiotic measures in transrectal biopsy

Non-antibiotic measures to reduce infectious complications include pre-biopsy rectal enema or rectal preparation with povidone-iodine. Pre-biopsy rectal enema appears to have no impact on rates of infectious complications/hospitalization (41, 159). Rectal preparation with povidone-iodine however has been shown to reduce both infectious complications and hospitalization (41). International guidance generally recommends using targeted or augmented prophylaxis alongside povidone-iodine rectal preparation (11, 181). EAU guidance however also strongly suggests considering the transperineal approach to reduce infectious complications (11).

Antibiotic prophylaxis in transperineal biopsy

In comparison to the transrectal approach, the risk of infectious complications in transperineal biopsy appears to be much lower with multiple studies reporting low rates of infectious complications with an incidence of sepsis ranging from 0–0.11% (53, 96, 97, 182–185). Whether antibiotic prophylaxis is required is an ongoing debate with its omission in some studies maintaining a low rate of infectious complications (1.9–3.6%) and no episodes of sepsis (90, 186, 187). A systematic review on the matter reported no significant difference in infectious complications for patients given antibiotic prophylaxis than those not with a pooled rate of infectious complications in the non-antibiotic prophylaxis group of 0.31% (185). Risk factors that have been identified for infectious complications in transperineal biopsy include diabetes mellitus and history of urinary retention (186). Interestingly, one study showed that asymptomatic patients with positive urine cultures pre-biopsy did not have an increased rate of urinary tract infection (188).

Urinary retention

Urinary retention is a risk of both transrectal and transperineal biopsies though transrectal biopsy appears to have a lower risk of retention than transperineal with one large UK population study reporting rates of readmission for retention at 1.9% vs 1% for transperineal and transrectal respectively (189). The figure of 1% for urinary retention post transrectal biopsy is supported by other literature reporting transrectal complication rates (182). There is a wide range of urinary retention rates post transperineal biopsy reported in the literature, between 0.05–10% with the lowest rates reported in local anesthetic freehand biopsies compared with higher rates in grid biopsies (87, 89, 90, 92, 181, 182, 185, 188).

Bleeding

Hematuria and hematospermia are common complications of transrectal and transperineal biopsies with rectal bleeding and perineal hematoma unique complications to transrectal and transperineal biopsies respectively (89, 184). Minor hematuria is common in both cohorts but significant bleeding requiring hospital admission is rare with similar rates reported for both approaches of around 1% (96, 183, 187, 189).

Concurrent use of antiplatelet and anticoagulant therapy

Concurrent use of aspirin during transrectal biopsies has been examined and systematic reviews have concluded that whilst it may increase or prolong minor bleeding, it is safe to continue, with an increase in risk of self-limiting rectal bleeding (190–192). The evidence on warfarin use during transrectal biopsies is limited by cohort size but several smaller studies report no increase in bleeding complications as a result of warfarinization (193–195). This suggests it may not be necessary to discontinue warfarin prior to biopsy, though a survey of urologists in 2010 found that 85% would do so routinely (196). Very little evidence exists to guide the use of novel oral anticoagulants (NOACs) such as apixaban and rivaroxaban, agents that are increasingly being utilized and as such further studies are required (197). Limited evidence exists for transperineal biopsy but in one study, in patients receiving antiplatelet or anticoagulant therapy, an increase in minor bleeding was noted but no severe bleeding events observed, though of note only a minority of patients were taking NOACs (198).

Erectile dysfunction

Erectile dysfunction is a common complication of both transrectal and transperineal biopsy. Systematic reviews report that prostate biopsy results in a decrease in erectile function at 1 month post biopsy which resolves spontaneously by 3–6 months, though the effect may persist slightly longer when biopsies are undertaken by transrectal as compared with transperineal approach (199, 200).

Needle tract seeding

Post biopsy seeding of cancer to the needle tract used during biopsy is incredibly rare. A review of the literature in 2015 identified 40 cases of this, 9 of these were taken via the transrectal approach and 31 via a transperineal approach. Seeding was generally seen in high grade disease. Of note, all of the transperineal biopsies were taken prior to 2000 generally using larger bore needles and although no correlation was observed by the authors in terms of needle devices, or diameter, it is fair to say that the approach used today is quite different (201).

Mortality

Death following prostate biopsy is rare, with rates up to 0.1% reported for both transrectal and transperineal biopsies. Additionally, studies have found that 120-day mortality rates in men undergoing prostate biopsies is no higher than in the control arm of men who did not undergo biopsy (202, 203).

CONCLUSION

Prostate biopsy is a key procedure in the diagnosis and risk stratification of prostate cancer. The transperineal approach is becoming more widely adopted

and increasingly under local anesthetic. Further developments in the field include an increase in targeting accuracy by the addition of robotic devices, however, there is a lack of evidence demonstrating the benefit of these at present.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter

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