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Mini Review

Challenges in Prostate Biopsy

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Abstract

Prostate cancer is a leading cause of death among US males. Great advances have been made in the diagnosis and treatment of prostate cancer. Particularly Prostate Specific Antigen (PSA) screening and the transrectal ultrasound-guided prostate biopsy (TRUS-BX) have been instrumental in achieving success in this field. This mini-review analyzes challenges in regards to the prostate biopsy and diagnosis of prostate cancer.

Keywords: *Imaging Guided Biopsy, Prostate Specific Antigen, Prostatic Neoplasms, Prostate*

Introduction

Prostate cancer is the second leading cause of death among males in the United States and remains the most prevalent cancer in the United States with almost 250,000 new diagnoses each year. The trans-rectal ultrasound-guided prostate biopsy has traditionally been the gold standard for the detection of prostate biopsy and is one of the most common urologic procedures performed. Approximately one million prostate biopsies are performed annually throughout the United States for the diagnosis of prostate cancer [1]. The procedure is generally well tolerated and has been found to have an acceptably low complication rate for the diagnosis of prostate cancer. The most common complications from prostate biopsy include infection, bleeding, urinary retention, erectile dysfunction and pain. Rarely, serious infectious complications from prostate biopsy result in Emergency Department presentation, hospital admission, sepsis, and even death [2]. The prostate biopsy, coupled with PSA screening is one of the great success stories in the war against cancer. Over the past 20 years since the advent of the PSA test, deaths from prostate cancer have fallen 44% to the current 30,000 per year [3]. Statistical models described by Etzioni et. al. attribute 45-70% of the decline in prostate cancer to PSA screening [4].

Despite this progress, recently the United States Protective Services Task Force (USPSTF) has announced its recommendations against PSA screening. This challenges Urologists, patients and primary care physicians to develop solutions to avoid reversing years of successful eradication of a deadly cancer. The USPSTF recommendations were based on several problems they wished to see addressed. First, the prostate biopsy does entail risk, most importantly that of infection. The recent rise in fluoroquinolone-resistant pathogens causing infection after prostate biopsy has led many authors to study effective ways to prevent and combat infection after TRUS-Bx [5-7]. Furthermore, the USPSTF was concerned that PSA screening required too many individuals to be screened in order to prevent a death related to prostate cancer, stating that 1000 men must be screened to present 1 death. Recent modeling studies suggest that the USPSTF likely overestimated the number needed to screen by 10-fold [3,8]. However, urologists must remain disciplined in how they counsel patients regarding utilization of the prostate biopsy to prevent over-diagnosis and overtreatment of less aggressive cancers. Prostate cancer is categorized by both clinical stage and cancer grade. Those patients with more advanced cancer derive more survival benefit than those with lower risk tumors [3,9-11].

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Several challenges must be addressed regarding the prostate biopsy, including improving the problem of overtreatment of indolent cancers, improving localization of cancers to reduce false negatives, and reducing the harms associated with the procedure.

Avoiding Over-Detection:
The over-detection problem can be addressed with use of multiple modalities in order to risk stratify patients. PSA is a good marker. A single PSA test at age 60 can predict prostate cancer death within 25 years with concordance index of 0.90 [3,12]. However, several researchers have looked at improving the test by incorporating different molecular markers and utilizing indices that incorporate more data (e.g. PSA doubling time). Discussion of each modality is outside the scope of this review; however, further study is warranted to determine if risk calculators, Prostate Health Index scores, PCA3 tests, and PSA density may help urologists develop better algorithms for which patients should get a biopsy. More restricted use of PSA screening in populations with lower life expectancy and tort reform may also be effective tools in reducing extra testing and preventing unnecessary biopsy rates [3,13].

Advances in Magnetic Resonance Imaging (MRI) have led this technology to play an increasingly important role in both the treatment and detection of prostate cancer. Current multiparametric MRI (mpMRI) technique involves evaluation of the prostate in multiple phases. The most commonly used phases are T2 weighted image (T2WI), diffusion weighted imaging (DWI) and dynamic contrast enhanced imaging (DCEI). These different phases are interpreted together to determine likelihood of malignant lesions in the prostate.

T2WI gives the best representation of zonal anatomy and cancer margins [14,15]. In this phase, prostate cancer appears low in intensity compared to the higher background T2 intensity of normal peripheral zone [16]. Transitional zone cancers are often described as heterogeneous in nature, lenticular in shape, lacking clear margins and capsule in T2 [17]. However, the sensitivity of T2 is often limited with a wide reported range, 27-100%, and specificities 32-99% [14]. This is due to patient and operator characteristics as well as being confused for benign pathology such as benign prostatic hypertrophy (BPH), prostatitis and hemorrhage after biopsy and post treatment changes [14]. A meta-analysis by Tan et al. found the overall sensitivity and specificity of T2WI to be 60% and 72% respectively [18].

DWI relies on the diffusion properties of water molecules at different intensities (b-values). (19) These images are then plotted and an apparent diffusion coefficient (ADC) is calculated. Prostate cancer tends to have a higher density than normal glandular tissue, resulting in a lower ADC value [19]. Jie et al. found an overall sensitivity and specificity of 62% and 90% in a meta-analysis of 21 studies. In a subgroup analysis of patients who underwent mpMRU with the use of an endorectal coil, sensitivity was increased to 77% [20].

The last phase of mpMRI is DCEI which consists of T1 images with contrast enhancement. DCEI relies on increased angiogenesis and therefore enhanced contrast uptake [19]. Peuch et al found DCEI to have a sensitivity and specificity of 32% and 95%, respectively, for any tumor, but with tumors larger than 0.5mL this increased to 86 and 94% [21]. This modality has been shown to increase the area under the curve (AUC) when combined with other modalities to enhance detection of prostate cancer [22].

With dedicated radiologists trained in mpMRI, the accuracy of detecting prostate cancer can be as high as 94.3% with accurate Gleason grading in 73.5% [23]. The interpretation of mpMRI is commonly conveyed to urologists in the form of Prostate Imaging Reporting and Data System (PI-RADS) score which uses a five point scale to express the degree of likelihood of cancer in specific areas and lesions of the prostate [16]. PI-RADS has been validated with biopsy data and a meta-analysis has shown an overall specificity of 79% and sensitivity of 78%, which included studies with patients with and without previous biopsies [24]. PI-RADS is reported on a scale of 1 through 5 with the significance of each shown below.

> PI-RADS 1: Clinically significant disease is highly unlikely to be present
> PI-RADS 2: Clinically significant disease is unlikely to be present
> PI-RADS 3: Clinically significant disease is equivocal
> PI-RADS 4: Clinically significant disease is likely present
> PI-RADS 5: Clinically significant disease is highly likely to be present

Improving Localization:
After the mpMRI has identified a lesion within the prostate, urologists can target these lesions in two different ways. One method relies on the practitioner to identify the lesion on MRI and then spatially recognize this lesion on trans-rectal ultrasound (TRUS) while performing the biopsy [25]. This relies heavily on practitioner experience and ability to visualize the lesion on ultrasound based on the MRI. This method, however, requires no additional equipment, making it easier to incorporate into already existing practices. The other method, MRI-fusion, involves incorporation of the MRI suspicious lesion into real time US [25,26]. The benefit of fusion technology is greater accuracy and increased detection of significant cancers [27,28]. A drawback of MRI fusion is the cost of the equipment and longer procedure time.

MRI targeted biopsies have traditionally been used for patients with an elevated PSA and previously negative biopsy [29]. Sonn et al. studied 105 men with prior negative biopsies and persistently elevated PSA who then underwent fusion biopsy. Cancer was found in 34% of these men, of which 72% were significant lesions [29]. In a study which included subjects with and without prior negative biopsies, 14.3% more cancers were detected with the use of fusion guided prostate biopsies [30].

In men without a prior biopsy, Park et al. found the cancer detection improved from 9.8% to 29.5% [31]. However, a randomized prospective trial in biopsy naïve men found no difference when comparing fusion biopsies and men receiving a traditional 10 to 12 core TRUS guided biopsy [32]. This study found no significant change in the rate of detection in prostate cancer (64 % vs. 57 %) or clinically significant prostate cancer (55 % vs 45 %) [32]. These studies suggest that mpMRI may have the greatest benefit in identifying lesions not readily targeted by standard biopsy.

An additional benefit of mpMRI guided biopsies may be in selecting patients who are good candidates for active surveillance (AS). However, the exact role of MRI for patients currently undergoing AS has not been defined. One potential use of mpMRI may be to screen candidates for AS protocols. Diaz et al. looked at patients who were being considered for AS who then received mpMRI with confirmatory fusion biopsy and found that 22.4 % were upstaged to a Gleason score ≥ 7 [33]. Additionally, the use of mpMRI fusion biopsy increased the rate of Gleason upgrading on subsequent biopsies from 13.8 to 29.3 % [33]. Another use may be in avoiding restaging biopsies in men undergoing AS. Siddiqui et al. retrospectively reviewed men who underwent fusion biopsies prior to undergoing AS and predicted that up to 68% of this population could be spared from the risks and discomfort of future biopsies [34].

Urologists who ultimately treat patients with prostate cancer have the additional benefit mpMRI prior to radical prostatectomy. A prospective trial of 104 men found that 27% of surgeons changed their operative plan from either nerve sparing to non-nerve sparing or vice versa with all having negative surgical margins on final pathological examination [35]. The use of mpMRI could accurately predict stage T3 disease in 59% with a sensitivity of 55.9% and specificity of 82.2% [36]. With the excellent spatial resolution, the use of mpMRI allows urologists to better plan robotic surgery where tactile feedback is limited.

A novel imaging modality for prostate cancer is Dynamic Contrast enhanced US (DCE-US) which consists of an injection of encapsulated microbubbles that travel into the microvasculature of the patient [37]. The increased angiogenesis of tumors take up this contrast to aide in the diagnosis and staging of prostate cancer [37]. In a prospective trial of patients undergoing prostate biopsy with DCE-US, 8.5 % of tumors were missed on imaging, with a sensitivity and specificity of 73 % and 56 % which increased to 91 % and 56 % when looking at Gleason ≥ 7 or larger tumors [38]. With the widespread use of US in prostate biopsies, advances in microbubble contrast represent an effective way to increase the accuracy of biopsies.

Reducing Morbidity:
Finally, efforts should be made to reduce the harms of the biopsy itself. Regarding the prostate biopsy, infection control likely represents the most important challenge faced by urologists. Several methods may be undertaken by urologists to keep infection rates low, including bowel cleansing, cleansing of operative equipment, and perioperative antibiotics. Bowel cleansing regimens to decrease bacterial counts have been associated with decreased infectious rates in a retrospective study of 879 patients by Jeon et. Al. The authors found the most significant influence on infectious complications was the use of pre-biopsy rectal preparation [39]. Further study can be done to ascertain how fecal colonies can best be eradicated via this mehthod. Cleansing of operative equipment has also been studied. The process for cleansing equipment was recently reviewed by Sabler et al. FDA sterilization guidelines were followed for processing the reusable trans-rectal ultrasound transducers and a contamination rate of 4.76% was found with no contaminations leading to symptomatic urinary tract infection [40]. The 2012 AUA Prostate Biopsy White Paper and the working group recommended cleansing along with steam sterilization as the preferred method for reprocessing prostate biopsy needle guides. However, they advised that high-level disinfection is still an acceptable alternative due to the lack of available data comparing each method [2].

Several different perioperative antibiotic regimens have been recommended. A common antibiotic regimen has been perioperative ciprofloxacin for 1-3 days. This antibiotic is generally well-tolerated and its effectiveness in reducing incidence of infection after prostate biopsy has been demonstrated in several studies [2,39]. Several authors have noted that the remaining infectious complications resulting from prostate biopsy are most commonly with organisms resistant to fluoroquinolones with Fluoroquinolone-resistant E.coli implicated as the most-common cause of sepsis following prostate biopsy [39].

Given the increasing incidence of fluoroquinolone resistance found in patients with infectious complications following prostate biopsy, some practices are exploring use of different antibiotics. Lange et. al reviewed a group of 24 men who presented with urosepsis after prostate biopsy and found that the organisms isolated from both the blood and urine were most sensitive to gentamicin [41]. Lorber et. al. found that a single dose of 240mg gentamicin during prostate biopsy was able to significantly reduce septic complications at a single institution [42]. Combination regimens have also been proposed. Luong et al. demonstrated a 0% hospitalization rate among 2041 patients undergoing TRUS BX utilizing a regimen consisting of 1 dose of oral ciprofloxacin 500 mg 1 hour prior to biopsy and 1g of intramuscular ceftriaxone peri-operatively. This regimen resulted in statistically significant fewer hospitalizations than a 3 day Ciprofloxacin regimen utilized in a similar patient population [43].

Another solution to the emergence of flouroquinolone-resistance proposed by some authors is the employment of screening methods in order to identify the patients most likely

to benefit from an alternative antibiotic regimen. Liss et. al. (2011) studied the use of rectal swab cultures prior to prostate biopsy to screen for resistance patterns prior to choosing an antibiotic regimen [44]. Duplessis et al performed rectal swabs on 235 patients and found that 32 had fluoroquinolone resistant bacteria and altered antibiotic therapy on these patients to reduce infection rate to 0 % [45].

One limitation to implementing this strategy would be the added logistical and financial burden involved with having each patient scheduled for biopsy present at least 48 hours prior to obtain rectal swab cultures. An alternative strategy would be to screen patients most at risk for flouroquinolone-resistance based on each patient's history and risk factors. Several studies have found an increased risk of faecal carriage of floroquinolone-resistant E.coli in patients administered fluoroquinolones during the 3-6month period prior to prostate biopsy and carriage of these strains has been shown to be a risk factor for infectious complications post-biopsy [46,47]. Recently, Liss, et. al. compared targeted prophylaxis to empirical prophylaxis in patients undergoing biopsy. In the former group, rectal cultures prior to biopsy were used to guide antibiotic selection. In the empirical group, ciprofloxacin was the standard antibiotic chosen. However, urologists added additional antibiotic prophylaxis to those patients seen to be at risk by their particular history. No statistically significant difference in sepsis rates was seen with an overall rate of post-biopsy sepsis of 0.5 % [48].

Despite the increase in resistance patterns among patients with infectious complications, fluoroquinolones still remain the standard antimicrobial prophylaxis during prostate biopsy. The 2014 AUA Best Practice Policy Statement pertaining to Prostate Biopsy recommends either using a fluoroquinolone or a 1st, 2nd, or 3rd-generation cephalosporin as a single dose [2]. Improvements can likely be made by utilizing rectal swabs or empirical prophylaxis. Screening for colonization can be timely and costly. A rapid, low-cost method for determining fluoroquinolone-resistance would be ideal. However, no test is currently available.

Other complications associated with prostate biopsy include pain, bleeding, and urinary retention. Generally the procedure is performed under only local anesthesia with the patient awake. The authors prefer to provide a periprostatic anesthetic block with lidocaine in order to minimize patient pain and discomfort with the procedure. With the patient in the left lateral decubitus position 22 gauge spinal needle can be inserted via transrectal probe to provide a periprostatic block. Care should be taken to insert the lidocaine at the lateral base of the prostate where the sensory nerves enter the prostate. The seminal vesicles join the prostate on either lateral border and can be used as a reference for providing the anesthetic block. Generally, the block is placed alongside the border of the prostate at the notch between prostate and seminal vesicles. With an anesthetic block, periprocedural and long term pain after the procedure is not commonly encountered and rates of

intolerable intraoperative pain of 0 % are reported in the literature [49]. Alternatively, 2 % lidocaine jelly may be applied trans-rectally at the beginning of the procedure or general anesthesia may be administered. While approximately 96 % of patients will report intraoperative pain during prostate biopsy, generally, pain levels are low with only 20-29 % of patients reporting severe pain or discomfort. Pain and discomfort during the procedure correlates with patient pre-biopsy anxiety. Therefore, every effort should be made to allay patient concerns prior to procedure [50].

Erectile dysfunction associated with prostate biopsy is poorly understood. In some series as high as 19 % of patients reported erectile dysfunction during the preoperative or postoperative period, which typically resolves by 30 days after the procedure in 50 % of the patients. Anxiety over the procedure and possible diagnosis as well as postoperative hematoma and neurovascular bundle disruption have been proposed as possible etiologies for acute-onset erectile function. All patients undergoing, TRUS-Bx should, therefore, be counseled on this possible side effect and erectile function should be assessed prior to biopsy [50].

Urinary retention and hematuria are also possible complications that may occur after TRUS-Bx. Each complication is relatively rare in the general population. Clinically significant hematuria occurring in only 1-3% of patients after biopsy [2]. However, patients with significant coagulopathies or on blood thinners should be identified for possibly being at higher risk [51]. Generally, the literature is too sparse to advocate for or against completing prostate biopsy while on Aspirin or anticoagulants such as Coumadin or Clopidogrel. However, consideration should be made towards stopping these medications perioperatively given the fact that prostate biopsy is not an urgent procedure [2]. Urinary retention occurs in approximately 0.2-1.1 % of patients. Patients with bladder outlet obstruction may be at increased risk for this complication and perioperative Alpha-blockade may be instituted to lower the risk of this complication [2].

The realm of prostate cancer and the prostate biopsy is a perfect arena for the application of the patient-physician relationship and tailoring the care provided to patient's individual preferences. The challenges urologists face may be overcome through factoring new imaging technologies, genetic disposition, family history, selective antibiotics prophylaxis, PSA and other markers, as well as patient risk tolerance to the care provided to patients.

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Authors Column

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