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Limitations of a Contemporary Prostate Biopsy: The Blind March Forward

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Abstract

In an attempt to reduce morbidity, focal targeted therapies and active surveillance have become increasingly popular treatment choices for localized prostate cancer. However, these modalities rely heavily on accurate and reliable tumor localization information provided by a prostate biopsy. Evidence that our contemporary biopsy techniques can do little more than detect some prostate cancers is notably lacking. What is meant by the accuracy and reliability of a prostate biopsy and why they are such important concepts to focal therapy and active surveillance are discussed.

Keywords

prostate neoplasms; prostate biopsy; localization; focal therapy; active surveillance

Fueled by the enthusiasm for PSA screening in the 1990's, urologists have, to date, focused primarily on the detection of prostate cancer.[1] This rather simple approach fit well with the therapeutic options of the period (external radiation, brachytherapy and radical prostatectomy), which always applied treatment to the entire prostate gland. However, contemporary changes in how we treat this condition now impose a higher expectation on the information provided by a prostate biopsy; namely, a shift towards focal therapy with an aim to lessen morbidity, and a revival in active surveillance as a preferred strategy.

Epistemologically, there are two diagnostic qualities that are desirable when considering a prostate biopsy: accuracy and reliability.[2] Accuracy refers to how close to the truth a diagnostic test is; whereas, reliability refers to how reproducible a test is. Furthermore, accuracy may refer to the grade, volume, or location of prostate cancer within the prostate and similarly, reliability may refer to each of these as well. We now consider each of these two diagnostic qualities as they apply to focal therapy and active surveillance requirements (Table 1).

Focal Therapy

Focal therapy is a rapidly emerging group of interventions that seek to treat prostate tumors locally while minimizing well-documented, adverse outcomes such as erectile dysfunction and

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urinary incontinence that occur frequently when the entire prostate gland is treated.[3] Subsumed in this paradigm is cryosurgery, HIFU and other emerging techniques such as photodynamic therapy.[4-6] While evidence of benefit is at best infantile, they have undergone rapid adoption.[7] A commonality to all forms of focal therapy is to limit the intervention to the 'diseased' area of the prostate, leaving the remainder intact, thus minimizing tissue injury. To do so, one needs to know where the cancer(s) is located within the prostate gland and more importantly, we need to know where the cancers are not. In effect, we want to know which areas in the prostate can be spared. In diagnostic terminology, we require a high specificity (high confidence that a negative sampling means there is no cancer in a particular area of the prostate).

In this regard, our prior work has pointed to the limitations of an extended template biopsy for localization.[8] Overall, 56.2% of men were found to have unilateral disease on an extended 12 core prostate biopsy; however, after evaluation of the radical prostatectomy specimen, only 40.4% of those with unilateral disease on biopsy actually had true unilateral disease. Moreover, the poor negative predictive value of tumor laterality of 24.7% and 31.3%, right and left side respectively, further points to the limited ability of prostate biopsy to exclude the presence of bilateral disease. Analyses examining even smaller regions of the prostate (eg left apex) revealed even lower specificity and negative predictive values. Taken together, our findings have dampened the enthusiasm for focal therapy, that is, until we improve diagnostic accuracy of prostate biopsy. To do so, we need to understand why a transrectal extended biopsy falls short.

Prostate cancer is commonly multifocal and microscopic requiring that we hit at least a few cancerous cell in only 10-12 needle cores.[8] One can liken this to the carnival game where you have to throw a softball into a round opening some 10 feet away. While that always looks easy, it never is, which is, of course, why carnivals can make money. Another explanation for poor tumor localization using a transrectal approach may be the systematic misclassification of tumor locations that are a function of taking needle cores at an angle oblique to the posterior surface of the prostate.[8] Conceptually, the needle path may pass from one area (eg prostatic apex) of the prostate into the adjacent area (eg mid prostate) and thereby sampling both regions. However, current labeling convention indicates only the site of entry into the prostate (eg prostatic apex). Therefore, when prostate cancer is identified on a biopsy pathology report, we really don't know if the cancer is in the prostatic apex or in the mid prostate area.

Biopsy strategies to improve specificity

The sextant pattern biopsy as first described in 1989[9] was considered the standard protocol for many years. However, several studies have recognized that the negative predictive value of sextant biopsy alone is poor[10-13]. To address this, urologists developed the transrectal saturation biopsy. Empiric data using this technique suggests that cancer detection is superior to traditional six or 12 core templates[14] although it is not merely a function of taking more needle cores[15, 16] nor is it of benefit as a initial biopsy approach. Moreover, the limited sampling of the anterior zone of the prostate (ie transition zone) still leaves much to be desired. An emerging technique, the transperineal saturation biopsy, has since been forwarded as a means to improve specificity.[17, 18]

In this transperineal technique, men are placed under anesthesia in the dorsal lithotomy position, as is done during brachytherapy, and biopsy needles are directed through the perineum under ultrasound guidance.[18] The needle paths are thus more parallel than perpendicular to the rectal surface and the anterior prostate may be sampled more readily. Furthermore, as the patient is anesthetized, a saturation biopsy 60-80 cores are usually taken. While this technique holds potential to overcome the sampling issue,[19] convincing evidence has yet to be published.

Others have chosen to focus on improving how the needle is directed into the prostate. An example of this is a computerized biopsy device which uses a flexible biopsy needle capable of bending 45 degrees when being directed into the prostate.[20] Coupled with a needle guide with a more acute angle, it is easier to limit the biopsy to the area of interest (eg prostatic apex or the mid prostate region). Reports to date, have suggested that prostate cancer detection using the flexible needle is likely comparable to other transrectal approaches but work to examine localization is still needed.[20] In the end, the ability of contemporary prostate biopsy techniques to fulfill the high specificity requirement for focal therapy remains unproven. Transperineal saturation approaches are likely an improvement; however, this comes at a cost given the requirements for anesthesia, operating room time and more extensive pathologic review. Future studies to quantify the incremental costs relative to potential benefits and harms (ie cost benefit analyses) have yet to be performed but are necessary to guide reimbursement and clinical practice.

Active Surveillance of low risk prostate cancer

A number of observational studies have confirmed the potentially indolent natural history of expectantly managed localized prostate cancer, particularly among older men with low- and moderate-grade tumors.[21] Recent reports of increases in the prevalence of definitive treatment among patients low-risk clinical characteristics have prompted renewed concerns about prostate cancer over-diagnosis and over-treatment.[22] As a result of this realization, physicians and patients alike are embracing the option of active surveillance for low-risk tumors.[23]

As with focal therapy, however, adoption of active surveillance imposes additional requirements on our biopsy techniques. In addition to the higher specificity discussed earlier, active surveillance requires precise localization of tumors (or at least the clinically significant tumors) within the prostate so that they can be ‘surveyed’ repeatedly and consistently. This, of course, refers to the diagnostic quality referred to as test precision or reliability. Evidence for biopsy reliability is even more limited than that for accuracy. Serial biopsy reports have shown that tumors may be missed in spite of repeated six-core sampling.[24, 25] Yet, in spite of this, a survey of French and Belgian urologists reported that 73% used prostate biopsies for tumor localization.[26] Indeed, to tackle the issue of reliability, we might begin with the following thought experiment on how we can ideally achieve 100% reliability.

Imagine for a moment that there is a patient with a single small focus of cancer in his prostate gland. Ideally, for active surveillance, we would take this prostate out, examine it under very thorough pathologic step-sectioning, noting the 3-dimensional location of the cancer focus, then replace the prostate into the patient. Then, we would apply our 3-dimensional information to a biopsy template that is able to direct a needle under ultrasound guidance to that exact focus of cancer. Aside from the obvious impossibility of this approach, our current technology does not permit such precise registration of cancer locations, not to mention that most cancers are multifocal and thus compounding the difficulty. So what can be done to improve the reliability of cancer localization?

Biopsy strategies to improve reliability

To improve reliability, we accept that most cancers are diagnosed using a standard transrectal extended biopsy template. One can then perform a transrectal saturation around the focus of cancer(s) but of course, this assumes that no cancer foci were missed at the initial diagnostic biopsy. Anecdotally, we have observed that repeated extended biopsies in men on active surveillance are likely to hit different tumor foci (easily seen when there is a difference in cancer grade or when the cancer is observed on the contralateral side). This is consistent with serial biopsy studies suggesting that tumor foci are missed quite often.[24] Another option is to perform a transperineal saturation biopsy where, as pointed out earlier, there are emerging data

to support accuracy; however, it is unlikely to be acceptable to most men to perform transperineal saturation biopsies repeatedly. Therefore, it may be reasonable to perform one transperineal biopsy after the initial detection of cancer for purpose of localization, then that localization data is registered to a computer model of the prostate. This computer model of the patient's prostate is then stored as clinical data and used when additional transrectal biopsies are performed. While this seems simple, practically, it has yet to be achieved. Currently, technology requires that the computer's simulated model of the prostate be registered to specific landmarks, eg prostate apex, base, lateral margins. It remains to be demonstrated whether this primitive landmark registration is sufficient to link up with a computer prostate model where the cancer has been found previously.[20]

Profound improvements in reliability can also be achieved with better engineering of the tools we use to perform a biopsy. In clinics today, we rely wholly on the surgeon's mental concept of a extended template implemented through manual guidance but future tools may do away with the surgeon altogether.[20] One such tool applies the use of computer directed biopsy template, in which needles are directed 3-dimensionally into the prostate, referenced to fixed points such as the apex, lateral edges and prostate base. It may not be too far-fetched to conceive of mini-Da Vinci robots that improve reliability by taking the ultrasound probe out of the surgeon's hand, fixing it to the floor, and by relation, to the prostate gland itself.

In moving forward, we need to improve our biopsy technology so that we can more accurately and reliably identify prostate tumors that need treatment. While modifications to ultrasonography including color flow Doppler imaging, bio-impedance, and contrast enhancement with microbubbles, have been proposed to improve localization of discrete tumors, they are still apt to miss small foci of disease[27-29]. Other promising techniques may be the co-registration of MRI images with the ultrasound image so that MRI abnormalities may be biopsied.[30] This, of course, is not likely to be helpful for the majority of prostate cancers, which are microscopic. Perhaps our greatest investment of research dollars should be in biomarkers and the linkage of biomarkers to ultrasound targeting. If certain molecular traits, eg TMPRSS2-ERG[31] are known to exist in most prostate cancers, then a tracer that linked to that molecular feature can be administered intravascularly making the tumor foci ‘light up’ on ultrasound. Proof of principle already exists, as molecular tagging is used in imaging modalities such as bone and prostascint scans. In the process, we must identify not only the best molecular marker but also merge that with ultrasound imaging techniques (eg microbubble contrast).

Taken together, the art of prostate biopsy is no longer just about detecting cancer, but rather about finding cancers accurately and precisely.[2] It is clear that our current transrectal approaches are insufficient for tumor localization. Failure to improve our biopsy techniques may lead many to be treated ineffectively with focal therapy or inappropriately left untreated with active surveillance. With that final thought, we must ask ourselves, “Can we afford to march forward blindly in the quest to conquer prostate cancer?”

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Table 1

Requirements for prostate biopsy accuracy and reliability as a function of treatment options

	Radical prostatectomy, external beam radiation, brachytherapy	Active Surveillance	Focal Therapy
Goal of prostate biopsy	Detect ANY cancer	Consistently sample known cancer foci	Rule out cancer in uninvolved regions
Need for accuracy/localization	N/A	Important	Important
Need for reliability	N/A	Important	Important*

* If treating less than one lobe of the prostate