Opening up new therapeutic avenues

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Prostate cancer remains the most common solid tumor diagnosed in American men. Approximately 220,000 men are expected to be diagnosed in 2016, representing approximately 25 percent of all new cancer diagnoses and approximately 9 percent of cancer deaths.[1]

The introduction of serum prostate specific antigen (PSA) screening in the 1990s resulted in a stage migration with most disease being detected at an earlier age, stage, grade, and volume.[2] Most men diagnosed in this fashion traditionally underwent treatment with whole-gland therapies, such as radical prostatectomy and whole-gland radiation, all of which significantly impact quality of life (QOL).[3-5] The paradigm of PSA screening, random prostate biopsy, and aggressive curative intervention of all cancers has resulted in a 40 percent reduction of prostate cancer mortality. While this reduction in prostate mortality is compelling, the lack of PSA specificity and random prostate biopsy to detect "significant disease" has resulted in unnecessary biopsy and treatment. The challenge providers face is to screen and detect "smarter" in order to minimize the burden of unnecessary biopsy and treatment. Ideally, the goal is to identify men who would benefit from aggressive therapy.[6-8]

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Improved Prostate Imaging with MRI

Recently, advancements in prostate cancer imaging using multi-parametric magnetic resonance imaging (mpMRI) have ushered in a paradigm shift for prostate cancer diagnosis.[9] Pelvic mpMRI combines anatomical T2 weighted sequences with diffusion weighted imaging (DWI) and diffusion contrast enhanced (DCE) sequences to localize regions of tumor suspicion within the prostate gland. The use of mpMRI vastly improves upon ultrasound prostate imaging by combining several magnetic resonance (MR) sequences to improve tissue evaluation and differentiation, leading to improved cancer detection and tumor localization within the prostate.[10-12] The sensitivity and specificity for detecting disease with mpMRI ranges from 70 percent to 90 percent and 61 percent to 89 percent respectively, with negative predictive values ranging between 85 percent to 95 percent.[13-18] Incorporating mpMRI into prostate cancer evaluation provides improved disease characterization for detection prior to biopsy, as well as for disease surveillance.[12,19]

Traditionally, prostate cancer is diagnosed through systematic random sampling of the prostate via transrectal ultrasound (TRUS) guidance. Yet TRUS biopsy sampling errors have lead to delayed diagnosis, understaging, and overdetection of low-risk disease.[20] Employing mpMRI prior to biopsy allows for targeting of regions suspicious for cancer.[21] Targeted biopsy can be performed via MR guidance, or via software-assisted MR-US (ultrasound) fusion techniques. Multiple studies have demonstrated improved detection rates for high-risk prostate cancer and decreased detection of low-risk disease when using MR-US fusion biopsy techniques.[22-24]

Improved imaging has opened avenues for image-guided therapies. Using MR-US fusion techniques similar to those used in targeted biopsy, energy ablative technology can now be targeted to lesions as focal therapy. There are many energy sources available to ablate prostate cancer. One such ablative energy source is high-intensity focused ultrasound (or HIFU), which offers novel opportunities for prostate cancer management.

MR-US Fusion Guided Prostate Biopsy

The use of TRUS guidance to sample prostate tissue has been a mainstay of prostate cancer diagnosis since the advent of prostate US imaging. While US imaging adequately defines the boundary

of the prostate, it does not provide accurate differentiation between normal and malignant prostate tissue. Thus, systematic prostate biopsies sample the gland in predefined regions, often using 10 to 12 biopsy core templates in order to sample the entire prostate.[25] Such sampling limitations hinder diagnostic accuracy and result in falsely negative results in up to 40 percent of biopsies. Furthermore, random sampling inadequately characterizes disease, leading to understaging and undergrading in up to 40 percent of men.[26-28]

Translating mpMRI findings to US targets requires specialized software and hardware. Several software and hardware platforms are commercially available.[29,30] Radiologists with expertise in prostate mpMRI interpretation prepare mpMRI imaging through software segmentation and demarcate predefined targets. This segmented mpMRI imaging is then registered to US imaging at the time of prostate biopsy, through a process known as MRI-US fusion. Real-time guidance and tracking of prostate biopsy then allows for targeted tissue sampling of mpMRI.[31]

One example of a commercially available MR-US fusion system is the Eigen Artemis® device. This fusion system uses encoders to track real-time location of prostate biopsies and features a robotic prostate biopsy arm to eliminate operator motion and ensure accurate targeted biopsy. The Artemis device can be easily incorporated into the urologist's usual biopsy workflow. In addition to targeted biopsy, the Artemis also provides spatial distribution of 12 core biopsy samples and tracks location of biopsy for men undergoing active surveillance or repeat biopsy.[32-35] In one of the largest published prospective studies of MRI-US fusion prostate biopsy, researchers at NYU Langone Medical Center reported improved detection of Gleason 7 and higher disease, as well as decreased over detection of Gleason 6 (low-risk) disease through the use of MRI-US fusion targeted biopsy.[23]

The Index Lesion: Defining the Treatment Target

The development of accurate prostate imaging—coupled with precise localization and identification of these image findings—has increased interest in minimally invasive ablative technology to destroy image-visible disease. Focal ablative therapy directs treatment to a precise lesion, otherwise known as lesion-based therapy. Limiting treatment to this lesion can minimize treatment effects to surrounding organs, including the bladder, urethra, rectum, and neurovascular bundles. For focal therapy to succeed, the nature and location of the lesion to be treated must be precisely understood.

Pathology studies confirm that up to 78 percent of prostate cancers on prostatectomy demonstrate multiple tumors and up to 86 percent exhibit bilateral disease.[36] The apparent multi-focal nature of prostate cancer has challenged implementation of focal therapy and serves as the basis for continued use of whole-gland therapy. However, a growing body of research supports the concept of the "index lesion." The index lesion—typically the largest tumor focus—is a single lesion, within the prostate gland that is the site of disease that poses metastatic potential.[37] The index lesion grade and stage predict risk for disease progression.[38] Several studies have demonstrated that the largest tumor by volume on prostatectomy specimen independently predicts biochemical progression.[39-43] Tumors found outside of this index lesion typically represent clinically insignificant disease. Correct identification of this index lesion provides the fundamental basis for focal ablation.[44, 45]

To further support the index lesion hypothesis, recent work by Liu et al. provides evidence that cells from a single disease site serve as the progenitor for metastatic disease.[46] As part of the Project to Eliminate Lethal Prostate Cancer (PELICAN), these researchers evaluated tissues from 30 men who died from metastatic prostate cancer with high-resolution genome wide evaluation of single-nucleotide and copy number polymorphisms. They demonstrated that metastatic sites could be tracked to a single precursor cell within the prostate. The goal of considerable research efforts: to prove that the progenitor metastatic cell stems from an index lesion are visible on mpMRI, further strengthening the oncologic premise of focal ablation.

HIFU: Focal Ablation of Prostate Tissue

Sound waves generated with a frequency greater than those perceptible by the human ear (frequency over 16 kHz) are considered ultrasound waves. These ultrasound waves can be projected into tissue and the measurement and display of the interaction of these ultrasound waves with biologic tissue provide the basis for diagnostic ultrasound imaging. As the ultrasound wave energy is increased, the energy imparted into tissue can result in biologic changes. When the energy is raised to greater than five Watts of power, the ultrasound becomes high intensity. High-intensity focused ultrasound, or HIFU, uses a dual-purpose transrectal ultrasound probe that allows for diagnostic imaging, but also allows for ultrasound energy to be imparted into tissue.[47] The energy ablation mode of the HIFU probe focuses ultrasound energy to a fixed point. Focused ultrasound energy consequently results in tissue absorption of the ultrasound energy, which is converted into heat. Temperatures exceeding 60 ºC can be obtained in a well-defined treatment zone, resulting in protein denaturation, coagulative necrosis, and cellular disruption. Secondarily, ultrasound energy absorption results in oscillation of micro-bubbles within tissue and leads to cavitation of these bubbles within tissue, resulting in further cellular destruction.[48]

The HIFU probe provides US imaging for localization of the target regions within the prostate and contains software to monitor local temperature effects on target tissue as well as surrounding tissue, such as the rectal wall. Through real-time treatment effect

monitoring and accurate image-guided planning, HIFU minimizes damage to surrounding tissue while achieving desired treatment effect to target tissue.

Currently one example of a platform available for HIFU in the United States is the Sonablate® 500 device. This device uses a dual ultrasound transducer (3 and 4 MHz) for both imaging and treatment. The procedure can be performed in an outpatient setting under general anesthesia and treatment is achieved entirely through a transrectal approach. The treatment is typically made in several zones, applying ultrasound energy in an anterior to posterior sequence. The urologist performing HIFU monitors treatment effects in real time and adjusts the treatment based on observations of the effects on tissue, such as cavitation and rectal wall temperature.

HIFU has been available in Europe and Japan for more than a decade and typically has been employed to ablate the entire prostate gland. Most studies evaluating whole-gland ablation report complications such as urethral stricture (19.7%), erectile dysfunction (34.9%) epididymitis (6.2%), incontinence (2.3%), and rectourethral fistula (0.1%).[49] In many cases, the morbidity of whole-gland HIFU ablation exceeded that of radical prostatectomy. Focal targeted HIFU promises to provide the ability to destroy a well-defined zone of the prostate harboring cancer with minimal impact on surrounding tissue, thus potentially decreasing side effects such as incontinence and erectile dysfunction.

As treatment zones become more precise and focused, morbidity decreases. In a recent study of men undergoing HIFU prostate hemiablation (ablation of half of the prostate), the 12 month pad-free continence rate was reported as 97 percent and 78 percent reported preservation of erectile function. While the cancer control results from this study suggest adequate treatment effects—89 percent of treated men undergoing surveillance prostate biopsy demonstrated absence of significant disease—these results remain immature and require further follow up as well as validation in larger studies.[50]

Combining MRI-US Fusion with HIFU: Improved Focal Targeting

Because of limitations in accurately targeting the site and the extent of prostate cancer, early studies of focal HIFU prostate ablation involved hemiablation treatment strategies. In order to minimize the complications associated with focal therapy, it is possible to target and treat only the cancer, with only a minimal margin of normal tissue included within the ablation zone. In this fashion, collateral damage to the neighboring structures is minimized. Such precise treatment requires an accurate definition of the location and extent of the index lesion needing ablation. The ablation must then be accurately targeted to this region with precise pre-planned treatment margins.

Current studies on mpMRI demonstrate that the index lesion is visible in up to 80 percent of cases.[51] Visible lesions can provide targets for MR-US fusion biopsy, allowing for reliable tissue sampling and disease mapping. The Artemis MR-US fusion platform then stores the location of targeted biopsies within the Profuse® software platform. The biopsy sites can then be mapped to the pathology results and a precise record of the exact tumor locations is created. This software also allows prior biopsy locations to be re-sampled on future biopsies, enabling re-examination of sites of disease and tracking of treatment efficacy. This feature allows for improved disease monitoring for men on active surveillance and also treatment effect monitoring for men undergoing focal ablation. With this software, the index lesion on mpMRI can be thoroughly sampled and surrounding tissue can be mapped.

The Profuse software is included with both the Artemis fusion biopsy devices and the Sonablate platform. Bridging the gap between biopsy and treatment, the software allows exportation of biopsy sites and fused mpMRI zones to the Sonablate 500 software, translating disease targeting to the treatment platform. At the time of focal HIFU ablation, the Sonablate 500 software can then perform MR-US fusion using real-time HIFU US imaging to fuse the index lesion location to treatment zones for targeted ablation.

NYU Langone Medical Center was the second tertiary center in the U.S. to offer focal HIFU ablation using the Sonablate 500. The combination of accurate mpMRI imaging with precise disease mapping via MR-US fusion biopsy requires multidisciplinary expertise in radiology and urology. Long-term data regarding cancer control through focal image-guided HIFU is being accrued; however, early data has demonstrated that the treatment does not impact sexual function or urinary control.

Future Challenges

While initial results are promising and providers gain experience with focal HIFU prostate ablation, challenges remain for improving focal therapy treatments. First, the current Sonablate 500 device is unable to accurately image and consequently map prostate glands much greater than 40 cm^3. In addition, index tumor location in the midline or anterior zone may present technical challenges for focal HIFU ablation. Also, the treatment margin needed to ensure complete index lesion ablation remains undetermined. While mpMRI appears to accurately visualize the index lesion, whole-mount pathology studies indicate that mpMRI imaging underestimates tumor volume.[52]

As focal therapy technologies advance, different ablative technologies may be required to optimally target and treat different lesions based upon size, location, clinical features, and proximity to critical surrounding structures, such as the apex, urethra, neurovascular bundles, or bladder neck. For example, bilateral HIFU prostate ablation may result in urethral sloughing and may pose a higher risk to urethral scarring and damage to the apex

as compared to focal cryotherapy, which uses a urethral warming catheter. Conversely, focal HIFU offers more precise treatment to peripheral zone tissue near the neurovascular bundler or rectal wall, while cryotherapy may result in less effective treatment in these zones given concerns over local treatment side effects.

Conclusions

More than 200,000 men will be diagnosed with prostate cancer this year. The majority of these men will be diagnosed with low- to intermediate-risk disease on systematic TRUS prostate biopsy using 10 to 12 randomly placed needles. These men face a complex and difficult decision regarding disease management. A properly performed multi-parametric MRI of the prostate will drastically improve the disease characterization for many of these men and can assist with proper treatment choice. Furthermore, including mpMRI prior to biopsy in the diagnostic pathway would further allow many men to avoid the inherent shortcomings of random systematic biopsy.

As access to quality mpMRI becomes more widely available, the prevalence of clinically localized and MR-visible disease will increase. Broader use of MR-US fusion targeted prostate biopsy will more accurately identify the index lesion in these prostates. Evolving from the foundation of accurate disease localization through imaging, and precise disease characterization via targeted sampling, focal ablation offers a promising next stage in prostate cancer management.

While many facets of this improved paradigm for prostate cancer detection, diagnosis, and treatment have yet to gain widespread availability, only a few centers of excellence currently offer expertise in mpMRI, targeted biopsy, and focal therapy, including focal HIFU. Through evidence-based application of these principles, focal therapy currently offers an attractive new option for men who meet proper selection criteria and are committed to rigorous follow up. As provider experience with these techniques and treatment options matures, we believe focal therapy will ultimately gain acceptance as an attractive, safe, and effective outpatient treatment option for a subset of men diagnosed with localized prostate cancer. OI

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