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Early detection of prostate cancer: can we have our cake and eat it too?

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Prostate cancer continues to remain the most polarizing of diseases. On one side, experts labor over the routine use of screening tools for early detection due to the risk of overdetection of clinically insignificant disease, thus leading to overtreatment and exposing patients to unnecessary morbidity. On the other, prostate cancer continues to be the second leading cause of cancer-related death in the United States (US) [1]. Central to this controversy is the inability to accurately assign risk due to the inherent lack of both spatial characterization due to sampling error and poor understanding of the biologic potential of both gross and microscopic disease [2].

Prostate specific antigen (PSA) as a screening tool has demonstrated the ability to improve early detection and decrease the incidence of advanced disease, corresponding to a decrease in prostate cancer mortality rates [1,3,4]. In two large randomized clinical trials, however, divergent results were reported with regard to the benefit of PSA screening and its impact on cancer-specific survival as compared to usual care. In the PLCO (Prostate, Lung, Colon and Ovary) screening trial, no significant improvement in survival was reported among the 76,685 patients enrolled [5]. However, in the ERSPC (European Randomized Study of Prostate Cancer Screening) 13 year update reported in Lancet last year, they reported a 21% overall reduction in prostate cancer mortality with PSA screening [6]. Irrespective, PSA testing remains limited by both its lack of specificity when within “normal” ranges and sensitivity when elevated above given cut-points, rendering patients either exposed to unnecessary diagnostic biopsies or lack thereof [7]. Molecular tests attempting to better stratify patients with a greater risk of occult and/or high grade malignancy during the initial screening period and after prior negative biopsies have been developed [8-10]. Urine assays such as Prostarix and PCA3, as well as the expansion of serum testing of human kallikrein molecules (4K and PHI) were introduced with the goal of improving upon this issue.

Despite these advances in molecular screening tools to identify at-risk patients for further diagnostic testing, another significant obstacle is the historically limited ability to image disease, undermining our ability for directed sampling or characterization of disease. The reliance upon random, nontargeted sampling of the prostate contributes to the controversy, raising concerns among patients and clinicians for the possibility of sampling error when noncancerous results are reported. Additionally,
significant morbidity has been attributed to the procedure of prostate biopsy, such as urinary tract infections and rare episodes of sepsis. All of these issues surrounding patient selection, sampling error, and the associated morbidity of diagnostics and overtreatment have ultimately led to the recommendations against PSA screening by the US Preventative Services Taskforce [11]. While this recommendation has been criticized by many specialists caring for patients with prostate cancer, more importantly it brought the limitations of accurate staging and grading of the true extent of disease to the forefront of the debate [12,13].

The conventional format for sampling of the prostate remains the central limitation in the stratification of disease risk. Multifocality remains the most common pattern of disease distribution, with solitary lesions occurring in 13% of patients [14-16]. The random sampling that is routinely implemented samples less than 1/1000th of the prostate volume. This has clear implications in the accuracy of genetic and molecular signatures in determination of risk when based upon random tissue samples, such as those utilized by Prolaris and Prostatvysion. Additionally, it largely focuses on the posterior aspects of the prostate, with the anterior gland being poorly sampled in larger volume prostates.

While ultrasound (US) characterizes cancer poorly within the prostate, MRI (magnetic resonance imaging) has improved upon this limitation in imaging of larger volume lesions. With the implementation of diffusion weighted and contrast enhanced prostate MRI, the ability to spatially localize dominant lesions has reduced the risk of understaging and even been proposed as a criteria to omit biopsy in prostate cancer patients on active surveillance [17-21]. However, many significant prostate cancers detected on random biopsies fail to reveal a targetable lesion on MRI when compared to radical prostatectomy specimens [22]. Fusion of archived multiparametric MRI images with live transrectal ultrasound has allowed for improved diagnostics and targeting. A recent publication from the National Cancer Institute reported on 1,003 men undergoing targeted and standard biopsies between 2007 and 2014 [23]. The primary objective was to compare detection of higher risk cancer of the prostate, with secondary objectives assessing detection of lower risk disease and predictive capabilities of fusion biopsies for whole gland pathology at time of radical prostatectomy. Overall, a 30% increase in the detection of high-grade cancers and 17% fewer low-grade
cancers were reported with fusion biopsy as compared to standard biopsy. Among those men proceeding to radical prostatectomy, a significant improvement in concordance with final pathologic findings was seen with targeted biopsy over standard biopsy. However, discordance between fusion biopsy results compared to final pathology was seen in 23% of cases, and in 47% of cases where standard biopsy techniques were utilized.

Again, the inherent limitation of this approach lies in their lack of sensitivity in the detection and prediction of the true extent of disease. In a recent publication comparing MRI/US fusion biopsies against cognitive MRI and 12-core sextant random biopsies, the detection rate of fusion biopsy with targetable lesions was just 35%, only slightly better than the 26.7% rate of detection for the combined cognitive and random sextant biopsies [24]. As the fusion software continues to improve, the accuracy of fusion biopsy will likely continue to improve. However, this modality still relies upon the use of needle samples to provide prognostic information on the risk assessment of patients. Several modalities have attempted to incorporate the use of molecular type imaging to fill this gap. Positron emission tomography (PET)/MRI; 11C-Choline, 11C-Acetate and 18F-Fluorocholine PET/CT (computed tomography), and PSMA SPECT/PET are all in the development for assessment of local and distant staging of disease [25-27]. However, resolution continues to hamper this technology at the level of the prostate.

Further technology continues to be developed. The goal of in situ imaging that allows for spatial localization of all disease present, while also allowing one to assess its grade and biologic potential, remains highly desirable [28,29]. The implications of developing this type of tool will be multifaceted, including the elimination of sampling error due to the reliance on needle biopsy and its resultant understaging of disease. This will open avenues for reliable approaches to targeted therapies, and limit the negative impact on diagnostic and treatment related morbidity. Until these technologies are fully developed and come to fruition in the clinical realm, we wait patiently and remain optimistic.
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