**Prostate Cancer: Defining Low Risk Disease for Active Surveillance**

Prostate cancer is the most common cancer in American men (excluding skin cancer), the second leading cause of cancer death with 1 in 6 men being diagnosed with prostate cancer in their lifetime. Prostate cancer is a disease of high prevalence and variable outcomes. Indolent cancer that pose no threat to a patient are extremely common. The current method of screening for prostate cancer consists of measurement of serum prostate specific antigen (PSA) and a digital rectal exam. If either is abnormal the patient goes on to transrectal ultrasound guided biopsy (TRUSBx). There are two problems with this approach. Firstly there is a problem of overdetection of indolent prostate cancer by PSA screening. It is estimated that 48 men are treated for prostate cancer for every life is saved when PSA screening is performed (1). The second problem is that the ability of ultrasound to localize prostate cancer is limited thus needle biopsies are done in a systematic fashion through the gland with 6,8,10 or more cores being taken. This understandably represents only a small volume of the prostate and can result in tumors being missed. It is estimated that 24% of cancers are missed after a 10 core biopsy (2). None of this would be problematic if it were not for the fact that current treatment strategies for prostate cancer carry morbidities that affect quality of life including sexual dysfunction as well as urinary and rectal dysfunction. An ideal imaging test should detect cancer to localize it for biopsy, have a high negative predictive value and also act as a (prognostic) biomarker of lethality of the cancer.

To address the concern of over treatment the current NCCN guidelines currently recommend active surveillance (AS) as a strategy for low risk prostate cancer. Active surveillance is defined as a disease management strategy that delays curative treatment until it is warranted based on defined indicators of disease progression (typically based on PSA, DRE, TRUSBx results). However up to 22-29% of patients eligible for AS still harbor life threatening cancer(3, 4). In addition there remains concern for disease progression while on active surveillance and missed opportunity for cure. As a result accrual into AS remains limited with as few as 10% of eligible patients electing for AS in the United States (5) and only 30% in Europe (6). Ten to 50% of these patients come off of AS over time because of anxiety or other causes unrelated to disease progression(7, 8). Thus imaging that could offer better patient selection on entrance into active surveillance, offer reassurance through a high negative predictive value for significant cancer through the course of surveillance and help define the optimal time for intervention would be ideal

**Multiparametric MRI**

Multiparametric MRI (MPMRI) has recently shown great promise in achieving the valued goals of a test for prostate cancer patients. MPMRI consist of T2 weighted imaging combined with one or more other MRI techniques such as DWI, MRS, DCE-MRI. There is a growing consensus that tumors >0.5cc that are Gleason score 6 or higher or tumors Gleason score 7 or higher are those that pose the most threat to patient and should undergo life treatment. For the localization of significant cancers MPMRI has had a sensitivity and specificity of ~80% in whole mount studies (9-11). Data specific to AS populations is limited but recent retrospective studies are showing great promise for MRI in this context (12, 13).

Both MRS(14) and ADC(15, 16) have also been shown to correlate with Gleason score. Gleason score is a pathologic parameter assessed on H&E stains and represents the single most important independent prognostic factor in prostate cancer thus MPMRI has the future potential to help guide patient selection for conservative therapy. Most recent data is suggesting that the ability of MRI to reliably detect Gleason 6 cancers may be poor due to the sparse nature of these tumors(17). This requires further
investigation as there is controversy in the uro-oncology community regarding the need to treat Gleason 6 disease.

How could MPMRI being used in Active Surveillance

The role of MPMRI in low risk patients is principally to exclude aggressive disease. It is not to detect all cancers. Thus patients with a negative MRI on entrance into AS would be expected to do well on AS. Should their PSA or DRE become abnormal or they reach a regular check point in surveillance they could undergo a repeat MRI to ensure no aggressive cancer has developed.

Although MRI is not part of the standard of care for AS patients we are now seeing patients being referred for MRI on entrance into AS. If the MRI is negative for cancer the patient enters AS with reassurance. If the MRI is positive they undergo a directed set of biopsies to see if there is high volume or high Gleason grade disease. For those patients on AS they often undergo a routine biopsy within the first three years or biopsy for cause (abnormal elevation of PSA or positive DRE). MRI is now being ordered to help direct biopsies in this scenario. Formal clinical trials in this context are needed.

The cost savings in deferring radical treatment and reducing the number of biopsy cores is a potential benefit especially if MPMRI can be shown to obviate the need for systematic whole gland biopsies. To achieve cost-effectiveness MPMRI without an endorectal coil or intravenous contrast would be of further benefit in reducing health care costs.

Summary and Challenges

MPMRI will likely have an important role in AS and may be the answer for the current paradigm of overtreatment in prostate cancer when added to current AS regimes. Prospective trials are required but may be difficult as MPMRI is rapidly adopted. At least standardization of image acquisition and interpretation are required to see this come into clinical practice and initial steps to achieve this are underway(18). The development of a stable quantitaive biomarker reflective of outcome or Gleason grade derived from DWI or MRS or some combination of imaging parameters would be of tremendous value as would be a measure of the NPV of MPMRI in the AS setting and this is a field ripe for translational research. There seems little doubt that the utilization of MPMRI is going to continue to grow in the management of prostate cancer.

References


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