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PI-RADS 4 or more: Active Surveillance no more

Running title: PI-RADS 4 or more: Surveillance no more

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Introduction

The introduction of multiparametric Magnetic Resonance Imaging (mpMRI) has improved the diagnosis and risk stratification of intermediate and high-risk prostate cancer. In addition to diagnosis, mpMRI has increasingly become a useful tool for monitoring prostate cancer risk of patients on active surveillance (AS) programs. A significant proportion of men on AS programs have suspicious lesions on mpMRI [1]. Accordingly, repeat mpMRI provides means of non-invasive assessment with the potential for fusion biopsy and preferential sampling of prostate cancer tissue.

In 2012, the Prostate Imaging Reporting and Data System (PI-RADS) introduced standardized reporting of prostate mpMRI. PI-RADS 4 and 5 lesions have been classified as “clinically significant cancer is likely to be present” and “clinically significant cancer is highly likely” respectively. PI-RADS 4 and 5 lesions are being increasingly correlated with intermediate and high-grade prostate cancer.

As recently discussed in: “*Gleason Pattern 4: Active Surveillance no more*” [2], patients with intermediate-risk prostate cancer are not suitable for AS. In light of this, the presence of PI-RADS 4 or 5 lesions on men enrolled to AS programs for prostate cancer warrants concern.

Active Surveillance is not suitable in intermediate-risk disease

It is now accepted that AS programs are safe in low-risk prostate cancers, with prostate-cancer specific survival of 98.1 and 94.3% at 10 and 15-year follow up respectively [3]. Conversely, recent literature suggests AS in intermediate-risk disease results in oncological compromise compared to radical treatment. Specifically, data from the PIVOT study identified a relative risk reduction of 31% in all-cause mortality in patients that underwent radical prostatectomy compared to those on AS programs [4].

In patients with intermediate risk prostate cancer, the enrolment to active surveillance programs implies an inherent risk of disease progression to metastatic disease. Klotz et al reported a large prospective active surveillance series of which 2.8% developed metastatic progression at 6.4-year follow up. Of the patients suffering metastatic progression, a vast majority were either initially diagnosed or upgraded to Gleason 7 disease [3]. In this intermediate prostate cancer group, other large prospective trials report risk reduction (up to 71%) in the development of metastatic disease after radical treatment compared to men on AS [4].

Indeed, the current body of evidence suggests that AS is not suitable for patients with intermediate risk prostate cancer due to increased risk of cancer progression and all-cause mortality.

mpMRI use in Active Surveillance

Among the major drawbacks to AS programs is the need for serial prostate biopsies to exclude tumour progression. Due to its minimally invasive nature, the use of mpMRI in men on AS programs is being recognized. Additionally, mpMRI is cost-effective and provides critical information on prostate tumour variables including location, size and presence of extra-prostatic extension. While there are potential benefits of mpMRI in this setting, there are several deficiencies that must be addressed. Firstly, at present there no robust clinical data to support the use of mpMRI alone in-place of repeat prostate biopsy in these patients [1]. Secondly, due to the lack of data, objective parameters for mpMRI findings have not been included as triggers for intervention in AS protocols. However, as evidence supporting the use of mpMRI accumulates, it may be assumed that such parameters may include quantitative values, such as ADC values or conspicuity measures [1]. Thirdly, some variability exists within mpMRI assessment including inter-assessor variability and non-concordance of MRI and histopathological findings of the tumour 'footprint'.

While current evidence is some-what limited, suspicious mpMRI in men on AS can accurately predict prostate cancer upstaging [5] and a normal mpMRI implies a low probability of intermediate or high-risk prostate cancer. It has also been demonstrated that stable mp-MRI correlates with stable Gleason scores in men on AS programs [6]. A recent systematic review concluded that mpMRI alone can detect clinically significant disease in a proportion of patients on AS [1]. Detection of PI-RADS 4 or 5 lesions during active surveillance warrants concern. There is an increasing body of literature outlining the risk of clinically significant prostate cancer with increasing PI-RADS scores. Previous reports suggest

that 70-90% of PI-RADS 4 lesions are graded Gleason >6 [7]. Grey et al recently published a report suggesting PI-RADS 4 lesions had a sensitivity and specificity of detecting clinically significant disease of 79% and 79% respectively following transperineal saturation biopsies. Pertinently, the risk of clinically significant cancer was significantly increased in patients with PI-RADS 4 lesions that were enrolled on active surveillance programs [8]. Sensitivity and specificity for identifying clinically significant cancers increase incrementally with the detection of PI-RADS 5 lesions. These findings are outlined in Figure 1 (adapted from data produced by Park et al [7]), with a case sample from our experience outlined in Figure 2.

In addition to the information provided via the PI-RADS scoring scheme, mpMRI provides the capability of performing targeted biopsy. Recent reports have demonstrated that mpMRI with possible fusion biopsy improves the detection of cancer progression in men on AS. Valerio published a systematic review and confirmed that 9.1% of clinically cancers were missed by transperineal saturation biopsies when compared to targeted biopsies[9]. Despite this, targeted biopsies miss up to 3.8 – 17% of significant prostate cancer [1]. Given this relatively high rate of missed significant cancer on targeted biopsy, many groups advocate for a combination of targeted and saturation biopsies for maximal safety.

Traditionally, while enrolled in AS programs, the identification of upgraded disease represents a trigger for intervention. Until formal recommendations regarding mpMRI are made, the authors suggest that the presence of PIRADS 4 or 5 lesions may represent a useful objective trigger for intervention, irrespective of corresponding targeted biopsy findings.

Conclusion

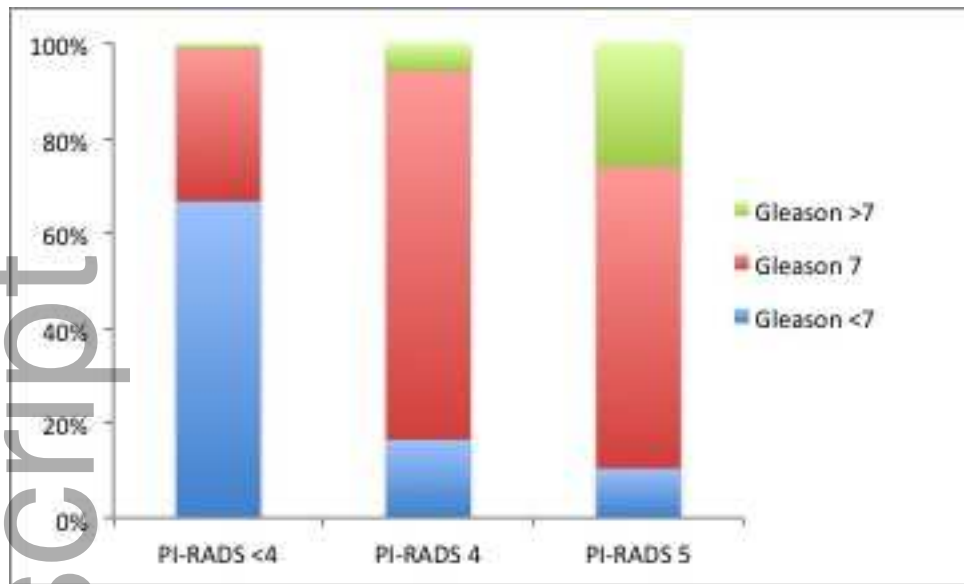
Long-term data indicates that there is no oncological benefit for AS programs with patients diagnosed with intermediate risk prostate cancer. Further, there is increasing evidence that PI-RADS 4 lesion on mpMRI correlates with intermediate and high-risk prostate cancer. Intuitively, PI-RADS 4 lesions may be considered a trigger for definitive treatment in patients on AS. Further improvements and experience in prostate imaging may provide the ability to sub-stratify these lesions and provide a more-tailored approach to PI-RADS 4 lesions.

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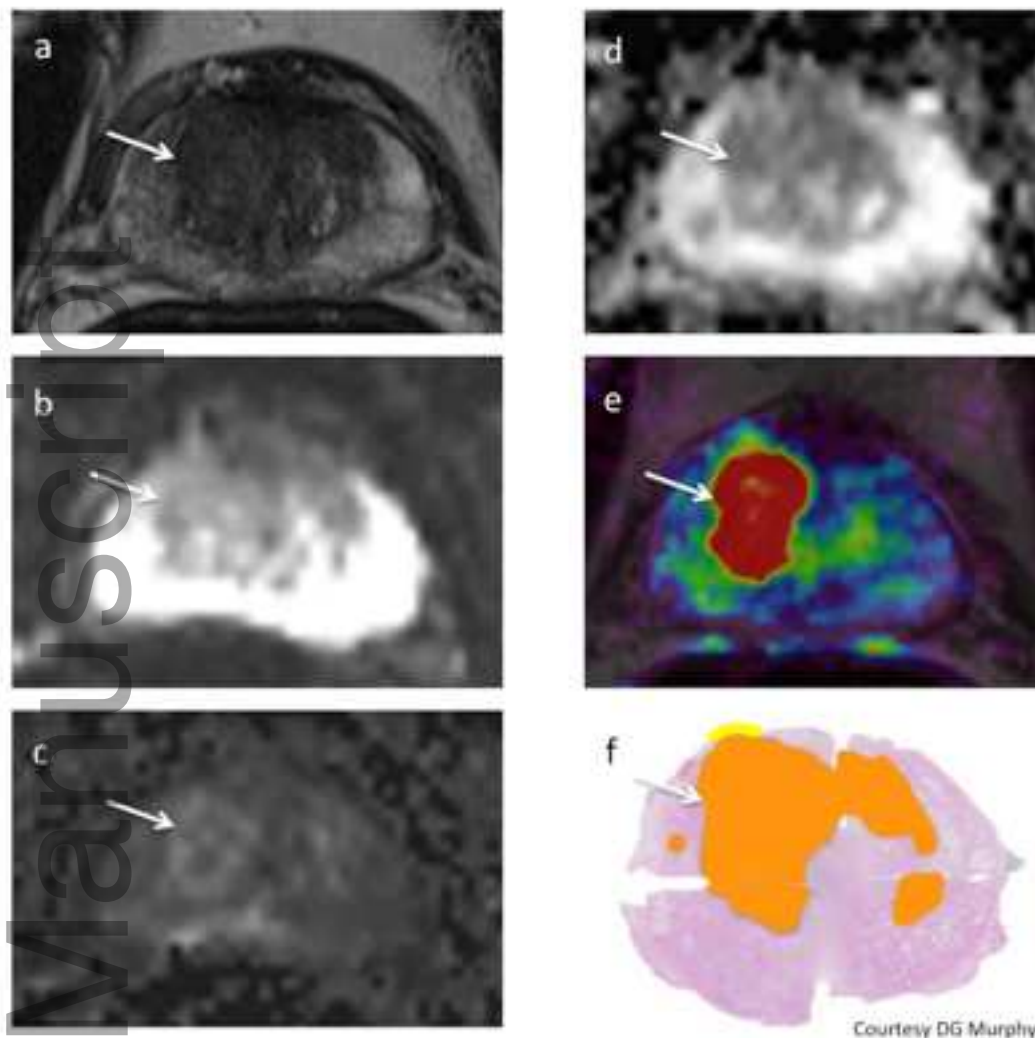
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Figure 1: Proportion of Gleason score stratified by respective PI-RADSv2 scores, adapted from Park et al [7].

Figure 2: This 64 year old male on active surveillance for low-risk prostate cancer, underwent mpMRI three months post-initial TRUS biopsy. This revealed a PIRADS 4 lesion in the anterior transition zone on the right side of prostate as defined by (a) decreased signal intensity on T2 weighted imaging, (b) restricted diffusion weighted imaging, (c) increased signal intensity on high b value diffusion weighted imaging, (d) ADC value of 900, and (e) focal contrast enhancement. He opted for robotic radical prostatectomy and the final histopathology (f) confirmed a pT3a Gleason 3+4=7 adenocarcinoma in a corresponding position.



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