Prostate Cancer Active Surveillance

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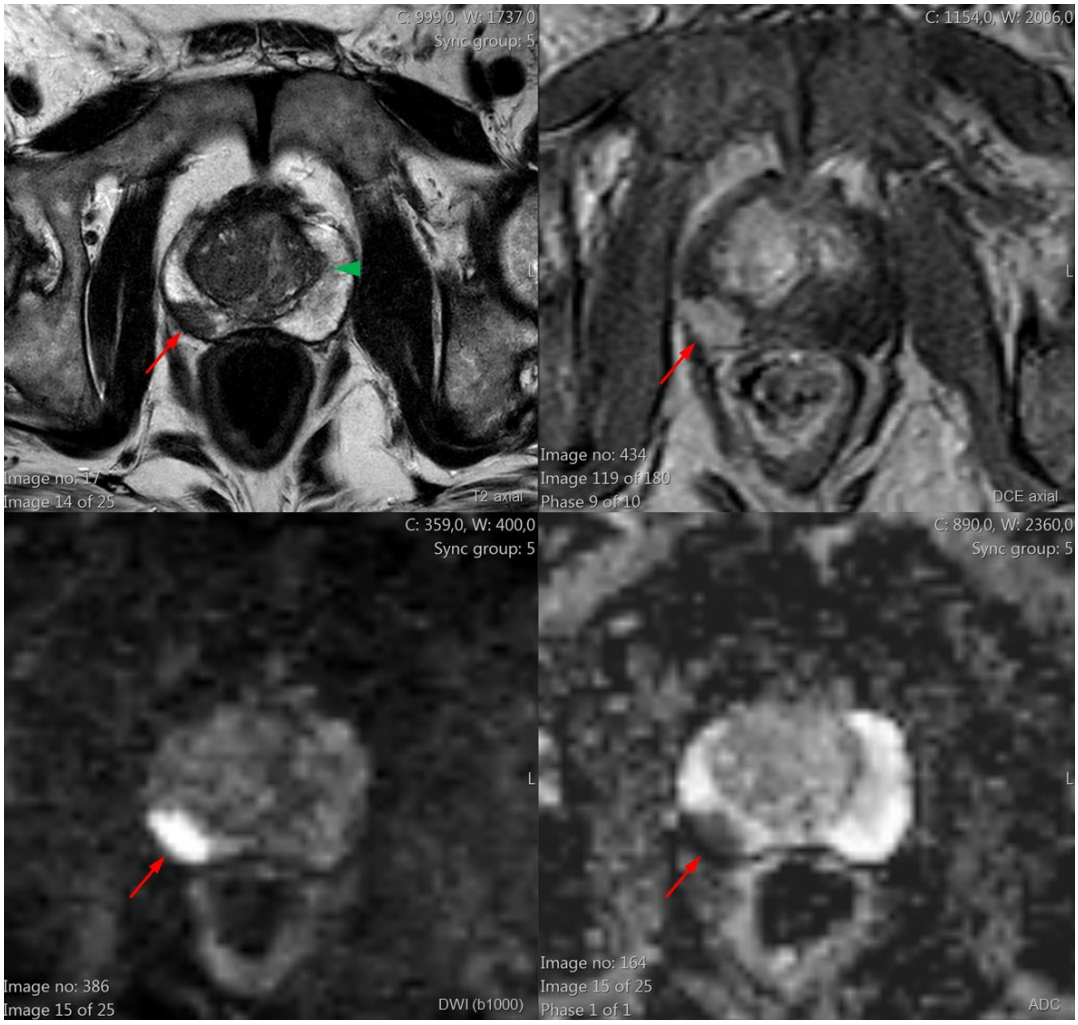
Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with a reported incidence of 1.1 million worldwide in 2012.[1] Ireland was estimated to have had the highest incidence of prostate cancer in Europe in 2006 which is expected to increase by 275% by 2025 based on current trends and our ageing population.[2] PCa screening remains a controversial topic in the urological literature.[3] A Cochrane review published in 2013 revealed that while PCa screening was associated with an increased diagnosis of PCa with detection of more low grade localised disease, no PCa-specific or overall survival benefit was demonstrated.[4] Issues have emerged in regards to the increasing incidence of insignificant cancers that are unlikely to influence lifetime prognosis. In order to combat the "overtreatment" of these cancers, Active Surveillance (AS) should be considered to reduce the morbidity inflicted by definitive therapies such as prostatectomy or radiotherapy.[5] While its use is most established in PCa, active surveillance is also considered in the treatment of low grade non-muscle invasive bladder cancers, uveal melanomas and certain pre-malignant conditions such as Barrett's oesophagus and gastric lesions.[6-8]

Since it was first described in 2002, AS has become a standard of care for low-risk PCa, particularly in patients with a limited life expectancy (<10 years).[9] AS involves the use of PSA testing, clinical examination, mpMRI imaging and prostate biopsies at regular intervals to closely monitor patients for disease progression, while simultaneously preserving quality of life and giving patients the assurance of definitive therapy if or when deemed necessary down the line.[9] Curative treatment is prompted by pre-defined thresholds indicative of potentially life-threatening disease that is remains potentially curable.[1] AS is generally reserved for patients with the lowest risk of PCa progression for whom radical treatment is suitable. The parameters for 'very low risk' and 'low risk' PCa outlined by the National Comprehensive Cancer Network (NCCN) are presented in Table 1.[1,10,11] Triggers for conversion to active management vary between centres but generally include a PSA velocity > 1 ng/ml/year, a Gleason score >7 and/or more than 50% positive cores on a repeat biopsy.[12] The impact of AS on PCa mortality has been studied with mixed findings. A very modest absolute difference was found in PCa mortality between patients undergoing active surveillance followed by radical prostatectomy versus those undergoing active management from diagnosis. A model proposed by Xia et. al suggested that the average projected increase in life expectancy associated with immediate radical prostatectomy was 1.8 months compared to AS, however men on AS would remain free of treatment for an additional 6.4 years in comparison.[13] The risk for tumour metastasis and death is



Figures 1 PCa mpMRI

Case courtesy of Dr Joachim Feger, Radiopaedia.org, rID: 73014, 72546

Red arrows: Large circumscribed, homogenous moderate hypointense focus, markedly hyperintense in DWI and markedly hypointense in ADC with early enhancement on DCE located in the right apical/midglandular posterolateral peripheral zone (PZpl)

Green arrow: Low signal intensity with obscured marings, isointense on DWI and markedly hypointense on ADC located in the eft basal/midglandular transition zone

low during active surveillance, with a rate of 4% and 0.5% respectively after ten years of surveillance.[14]

The 'National Clinical Guideline for the Diagnosis, Staging and Treatment of Prostate Cancer' published by the NCCP in conjunction with the NCEC in 2015 offers clinicians a protocol for men who have opted for active surveillance in the management of their PCa.[10] The first five years of this protocol are presented in Figure 3. Upon reaching five years of progression-free survival, the patient should continue with six-monthly clinic visits with biopsies suggested every three years until either radical treatment is initiated, the patient reaches 75 years of age, the patient switches to an alternative 'watch and wait' protocol or until death.[1,10] These guidelines are often considered to be outdated as they fail to incorporate PSA-density, which has been shown to have improved sensitivity when compared to standard PSA testing.[15] New up-to-date guidelines are currently in development, placing more emphasis on the use of mpMRI, PSA-density and transperineal biopsy.

Prostate-specific antigen (PSA) is a serine esterase produced almost exclusively by the prostatic epithelium. While its use as a tumour marker has been established over the last thirty years, it is not specific for PCa and has a high false positive rate when used as a screening tool.[2] Prostate-specific antigen density (PSAD) refers to the ratio of PSA level (ng/mL) to the volume of the prostate (mL) and is more specific to PCa than standard PSA testing.[16] As PSA alone can be raised in a variety of both benign and malignant conditions, PSAD is more commonly employed in everyday practice to both detect new and surveil known prostate cancers.[17]

Multiparametric MRI (mpMRI) of the prostate is a novel promising tool for the diagnosis of PCa which may aid the reduction of overdiagnosis and overtreatment of insignificant prostate cancers.[18] The incorporation of mpMRI into the diagnostic pathway has helped to address the inadequacies of trans-rectal ultrasound (TRUS) guided biopsies in detecting PCa.[19] mpMRI uses four sequences; T1-weighted images, T2-weighted images, diffusion-weighted images (DWI) and dynamic contrast-enhanced imaging (DCEI). Interpretation and reporting of these images is carried out using standardised scoring systems including 'Prostate Imaging Reporting and Data System (PI-RADS).[18] Several studies have been conducted to determine whether mpMRI could correctly identify patients suitable for active surveillance. In 2013,

TABLE 1: NCCN PCA RISK STRATIFICATION[11]

PARAMETER	VALUE		DESCRIPTION
	Very low risk (All of the following)	**Low risk (All of the following)**	
TNM STAGE	</= cT1c	T1-2a	T1c: Clinically inapparent non-palpable tumour identified by needle biopsy T2a: Tumour contained to less than half of one lobe
PSA	<10 ng/mL	<10 ng/mL	Prostate specific antigen; raised in both benign and malignant conditions
BIOPSY GLEASON SCORE	</= 6	</= 6	Histological classification based on degree of glandular de-differentiation. Scored from 2-10 based on two most common cellular morphologies
POSITIVE CORES	</= 3	-	</= 2 cancer-containing biopsies out of all biopsies taken (~10-12)
CORE INVOLEMENT	<50% cancer per biopsy	-	Proportion of positive core containing tumour cells
PSA DENSITY	<0.15 ng/mL/g	-	Ratio of PSA level (ng/mL) to the volume of the prostate (mL)

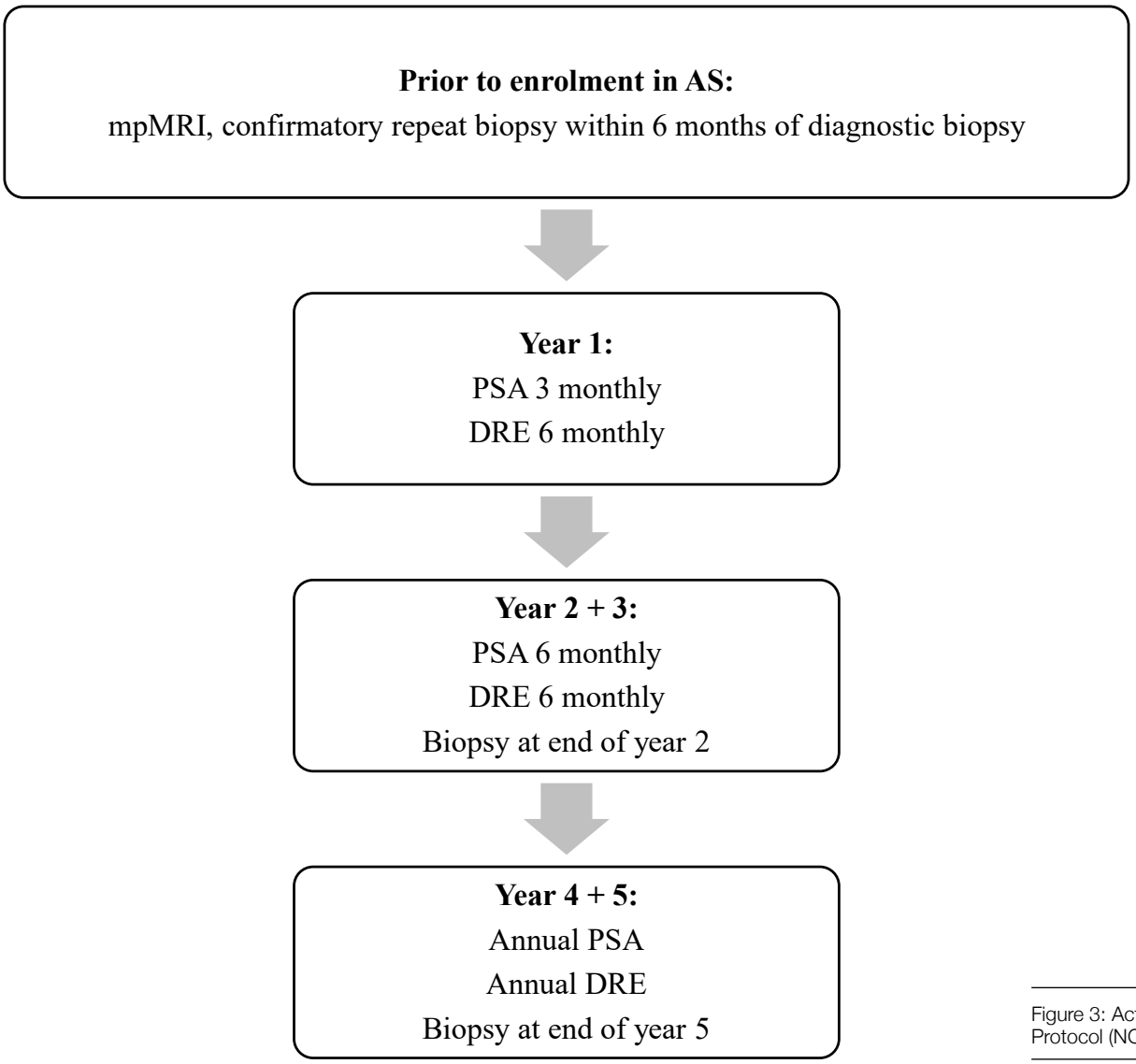


Figure 3: Active Surveillance Protocol (NCCP/NECP 2015)

Turkbey et. al compared mpMRI to various other clinic-pathological criteria such as CAPRA, Einstein and D'amico to predict active surveillance eligibility. Results showed that mpMRI proved to be the most accurate in doing so, with an overall accuracy of 92%.[20] Similarly, the 'Active Surveillance magnetic resonance Imaging STudy' (ASIST) trial revealed 50% fewer active surveillance failures in patients who received a baseline mpMRI prior to confirmatory biopsy than patients who received biopsy alone.[21] While mpMRI has evidently improved the selection of patients for active surveillance, there is a lack of evidence to suggest that it can safely replace surveillance biopsies in this cohort.[19] Recently, targeting the prostate-specific membrane antigen (PSMA) with 68Ga-labelled and 18F-labelled PET-agents has demonstrated superior detection efficacy compared to standard of care imaging of biochemically recurrent PCa. This modality has shown to significantly aid the detection of otherwise occult nodal and bone metastases, which may have a substantial impact on subsequent treatment decisions and patient outcomes.[22,23]

Prostate biopsy remains the gold standard technique for the detection of PCa, however mpMRI and PSA-density testing appear to be the optimal methods of surveillance.[24] Ultrasound (US)-guided biopsy is the current standard of care and is performed via either a trans-rectal or trans-perineal approach.[1] While both the transperineal and transrectal approach appear to have a similar diagnostic accuracy, the transperineal route has been associated with a significantly lower risk of infection and bleeding and is employed almost exclusively in the United Kingdom.[25] A trans-rectal US probe is used to guide the needle into the prostate where twelve core biopsies are taken.[24] Contemporary MRI-guided strategies have been used to allow more selective sampling of lesions previously identified as suspicious on mpMRI. mpMRI data is mapped to a T2-weighted scan obtained prior to the biopsy and a biopsy needle is used to target these areas of high suspicion. This approach has been shown to be effective in detecting cancer in patients with a rising PSA but previous negative TRUS-guided biopsy.[26] A confirmatory transperineal biopsy may also be performed following the initial diagnosis of low risk PCa on TRUS-guided biopsy, as evidence suggests that approximately one-third of low risk PCa diagnosed on TRUS-guided biopsy actually have more significant cancer on a subsequent transperineal template biopsy.[27,28] In our practice, a confirmative transperineal biopsy would be performed after one year of active surveillance in patients with low risk disease on TRUS-guided biopsy with concordant MRI findings.

Prostate cancer is on the rise in Irish men.[2] As PSA screening becomes more accessible, more early stage localised cancers are being diagnosed. It is essential to combat the unnecessary overtreatment of these cancers by implementing an active surveillance protocol in suitable patients in order to both maintain an adequate quality of life as well as reduce treatment-related morbidity and mortality.

References upon request