THE ROLE OF MULTIPARAMETRIC MRI IN PATIENTS ON ACTIVE SURVEILLANCE FOR PROSTATE CANCER: ASSESSMENT AND VALIDATION OF THE PRECISE RECOMMENDATIONS

Thesis submitted to University College London

for the degree of Doctor of Philosophy

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I, Francesco Giganti, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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A journey of a thousand miles begins with a single step

(Lao Tzu)

Abstract

Introduction: Magnetic resonance imaging (MRI) of the prostate can identify candidates for active surveillance (AS), who can safely be monitored to allow prompt curative treatment if the disease shows signs of becoming more aggressive.

Methods: We established the guidelines for the reporting of MRI in AS, known as the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations. The key features are the measurement of each lesion at every time point, and a determination of the likelihood of radiological progression according to changes in tumour size and conspicuity using a 1-to-5 scale (PRECISE score). I evaluated the impact of Dutasteride on tumour conspicuity on MRI. I applied the PRECISE score at University College London Hospital (UCLH) and analysed the inter-observer variability at two different centres. As prostate MRI quality is key during AS, I created a new scoring system (PI-QUAL) to assess image quality.

Results: Dutasteride affects tumour conspicuity on diffusion-weighted imaging. Freedom from clinical progression (i.e., progression to ≥ Gleason Grade Group 3 or initiation of active treatment) at 60 months in the UCLH cohort is 97% for PRECISE 1-2 (radiological regression) and PRECISE 3 (radiological stability), while only 61%, for PRECISE 4-5 (radiological progression) ($p<0.001$). There is a significant difference in the average yearly percentage volume change over time stratified by PRECISE score using the ellipsoid formula. The inter-reader reproducibility of PRECISE is substantial ($\kappa = 0.71$ and agreement = 79%). PI-QUAL is a promising scoring system (1-to-5 Likert scale) to assess the diagnostic quality of MRI.

Conclusions: Patients without radiological progression (PRECISE 1-3) during AS have a very low likelihood of clinical progression and many could avoid routine re-biopsy. The inter-reader agreement of PRECISE is substantial. PI-QUAL represents the start of identifying a framework for the assessment of prostate MR quality.

Impact statement

Magnetic resonance imaging (MRI) can identify candidates with localised prostate cancer suitable for active surveillance but from a radiological point of view it is challenging to determine progression during active surveillance. This thesis describes the important steps that have been recently done at this regard by evaluating the feasibility of the PRECISE scoring system in patients with prostate cancer on active surveillance undergoing serial prostate MRI.

The findings of this work are directly applicable to clinical practice, as the PRECISE score can identify patients on active surveillance who are progressing radiologically (i.e., PRECISE 4 - 5) in a timely manner. This work also has the potential to improve quality of life, as patients with stable findings (i.e., PRECISE 1 - 3) on MRI could avoid repeat biopsy, reducing the burden of surveillance for the individual and the healthcare system.

This thesis also assesses the role of a dedicated tool to facilitate reporting in accordance with the PRECISE recommendations. This software augments the radiologist's expertise in identifying the suspicious areas on MRI and reduces the amount of time to report serial MR scans during active surveillance, producing at the same time a structured report in line with the PRECISE recommendations.

This works brings also new knowledge on the impact of medications such as Dutasteride on the appearance of prostate cancer on MRI during active surveillance.

Finally, this thesis addresses the important topic of image quality in prostate MRI, focusing on a new scoring system (PI-QUAL score) to assess the quality of prostate

MRI, which is essential for the evaluation of radiological change on serial scans during active surveillance.

This thesis has strengthened multidisciplinary ties with the medical specialities of urology, radiology and radiation oncology at an international level.

This work has also promoted collaboration with industry, which will undoubtedly help in the development of novel tools that can assist the radiologist during reporting and, ultimately, benefit patient care.

The work presented in this thesis has laid the foundations for future collaborations and for the refinement of the PRECISE score (cited 134 times according to Google Scholar at present). It has also allowed further research on optimising the diagnostic quality of prostate MRI and has promoted further research into this aspect. The results from this work add to the growing evidence that will influence the relevant international bodies to include prostate MRI (and the PRECISE score) in the active surveillance pathway of their prostate cancer guidelines.

In conclusion, this thesis explores evidence that MRI can be used to assess stability or identify any sign of progression of prostate cancer in patients on active surveillance and highlights the importance of MR images of optimal diagnostic quality, especially in the active surveillance setting.

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Chapter 1 Introduction

Some of the findings presented in this chapter have been published in:

- *Giganti F, Rosenkrantz AB, Villeirs G, et al. The Evolution of MRI of the Prostate: The Past, the Present, and the Future. AJR Am J Roentgenol (2019); 213(2):384-396.*

- *Giganti F, Moore CM. MRI in early detection of prostate cancer. Curr Opin Urol (2019); 29(6):563-568.* [54]

1.1 Prostate cancer epidemiology and risk factors

Prostate cancer is the second most commonly diagnosed cancer worldwide with an estimated 1,300,000 new cases per year and the fifth leading cause of cancer death in men. [1] It is also the most commonly diagnosed solid organ cancer in men and the second commonest cause of cancer death in the UK, with around 40,000 cases diagnosed each year. [2]

Overall, almost 97% of men survive prostate cancer for at least one year after diagnosis but this falls to 86.6% for five years or more, as shown by age-standardised net survival for patients diagnosed with prostate cancer during 2013-2017 in England. [3] The survival continues to fall beyond five years, as 77.6% of men are predicted to survive for ten years or more. (Fig. 1)

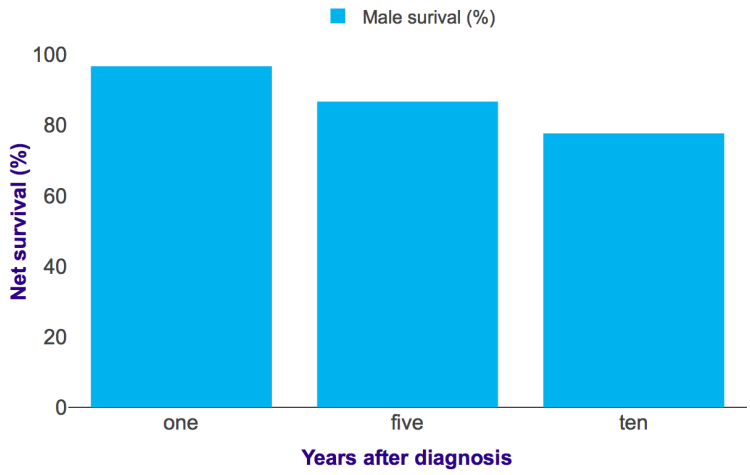

Fig. 1 *- The blue bar charts show one-, five- and predicted ten-year prostate cancer age-standardised net survival rates for adults (aged 15-99) in England (2013-2017). Reproduced from Cancer Research UK (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/survival#ref).*

However, prostate cancer survival depends on the clinical stage at the time of diagnosis. Those men with localised disease have a five-year relative survival of 100%, compared to 31% for those men with distant metastases at the time of diagnosis. [4]

An important aspect of prostate cancer is the significant variation in the incidence worldwide. The highest estimated rates are in the higher resource countries of the world including Australia/New Zealand, Western Europe, North America, and the Caribbean. The lowest rates are in south central Asia, northern Africa, and eastern Asia. [5] (Fig. 2)

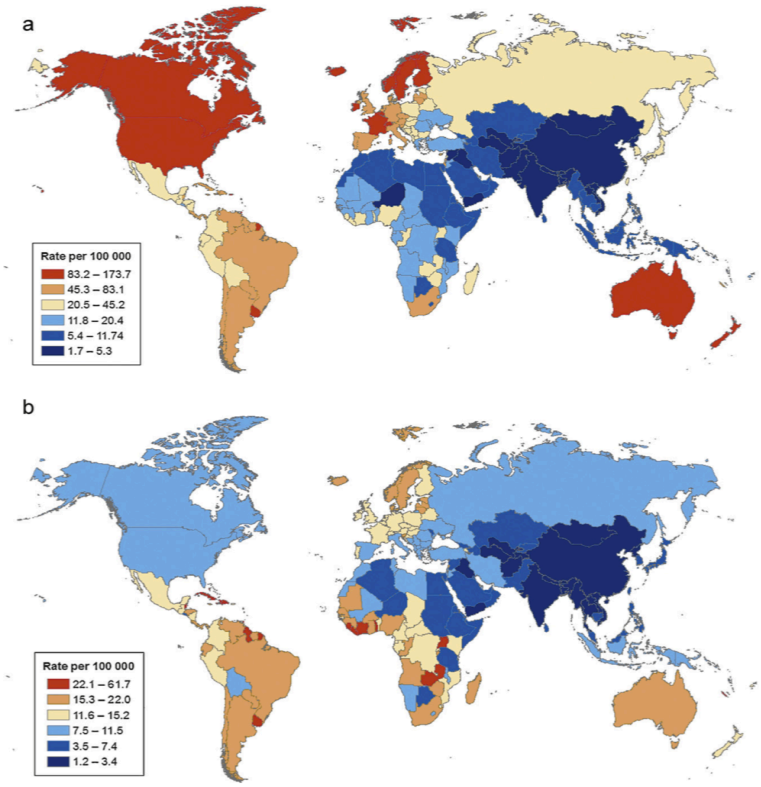

Fig. 2 *- International variation in age-standardized prostate cancer incidence (a) and mortality (b) rates. Reproduced with permission from Center MM, et al 2012.* [5]

The differences in incidences among countries are impacted significantly by race and by the diagnostic practices applied in each country.

One of the main reasons is that the use of prostate specific antigen (PSA), a serine protease mainly produced by prostatic epithelial cells, as a diagnostic test for prostate cancer is more frequent in higher income countries and it is known that widespread use of community PSA testing increases the detection of prostate cancer up to 80% compared to the use of digital rectal examination (DRE) alone. [6,7]
We know that without screening many cases of prostate cancer do not ever become clinically evident, as prostate cancer often grows so slowly that many men die of other causes before the disease becomes clinically advanced. [8]
Therefore, the variation in the incidence of prostate cancer between countries is largely due to the differences in the diagnostic tests used, as the more resourced countries show greater use of PSA testing and transurethral resection of the prostate (TURP), with subsequent incidental diagnosis.

There are three well-known risk factors for prostate cancer: i) age (peak in the 75-79 age group); ii) ethnicity/race (lifetime risk is 13.2-15% for White males, 23.5-37.2% for Black males and 6.3-10.5% in Asian males) and iii) family history of prostate cancer. [2]

There have been around 50,000 new prostate cancer cases in the UK per year (2015-2017), which means more than 130 every day. Incidence rates are projected to rise by 12% between 2014 and 2035, to 233 cases per 100,000 males by 2035, and this is also the result of the celebrity endorsement (in February and March 2018)

of cancer awareness and screening (i.e., heightened public use of healthcare resources and referral pathways), although it should be acknowledged that after an initial 25% rise in referrals and diagnosis the average rate has remained stable. [9]

UK data show that Black men have a similar outcome (stage for stage) compared with the white population. [10]

There is also evidence that a family history of prostate cancer is associated with the development of this disease. Men with one first-degree relative (i.e. father, brother or son) diagnosed with prostate cancer (especially for aggressive disease diagnosed at a young age) suffer an increased risk (relative risk: 5.51 for a father and a brother) of developing the disease, and this increases further in men with two brothers (relative risk: 7.71) diagnosed with prostate cancer. [11]

There are also some germline mutations that have been identified amongst men with non-hereditary prostate cancer, including some genes mediating DNA-repair processes such as Breast Cancer gene (BRCA) 1 and 2. [12]

1.2 Classification and staging system of prostate cancer

1.2.1 Tumour, Node, Metastasis (TNM) staging

The Tumour, Node, Metastasis (TNM) staging method was first implemented in prostate cancer in 1992, when the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) adopted a unified staging system. [13]

Since then, many revisions have been kept it up to date. Clinical stage only currently refers to DRE findings, while both the imaging and pathological TNM staging systems are based on the corresponding findings on imaging and histology specimens, respectively.

Table 1 (next page) summarises the clinical TNM (cTNM) staging system for prostate cancer.

Pathological staging (pTNM) is based on histopathological tissue assessment. All histopathologically confirmed organ-confined prostate cancers after radical prostatectomy are pathological stage T2 and currently UICC no longer recognises pT2 substages. [14,15]

Table 1 *- Clinical Tumour Node Metastasis (cTNM) classification of prostate cancer*

T - Primary Tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

1.2.2 Histopathological characteristics of prostate cancer

Three major criteria are used to describe prostatic adenocarcinoma, which is the most common pattern of prostate cancer. These are: i) glandular architecture; ii) basal cell loss; iii) nuclear atypia. [13]

Prostatic adenocarcinoma shows an aberrant glandular architecture, with disruption of the normal relationship between epithelium and stroma.
Five stages of gland growth are used for prostate cancer and they are named Gleason scores after Donald Gleason, an American pathologist, who developed this scoring system in 1966. [15]

The Gleason grading system is based entirely on the histologic pattern of arrangement of carcinoma cells in haematoxylin and eosin-stained prostatic tissue sections: the higher the Gleason pattern, the more poorly differentiated the tissue and the more aggressive the cancer. [15] (Fig. 3, next page)

The original Gleason grading system has undergone several modifications, endorsed by the International Society of Urological Pathology (ISUP) in 2005 and 2014. [16,17] (Fig. 4, next page)

Among these, it was agreed that Gleason pattern 1 and 2 should no longer be reported on biopsy and that a broader Gleason Grade grouping system ranging from 1-5 should be used, as shown in Table 2 (next page).

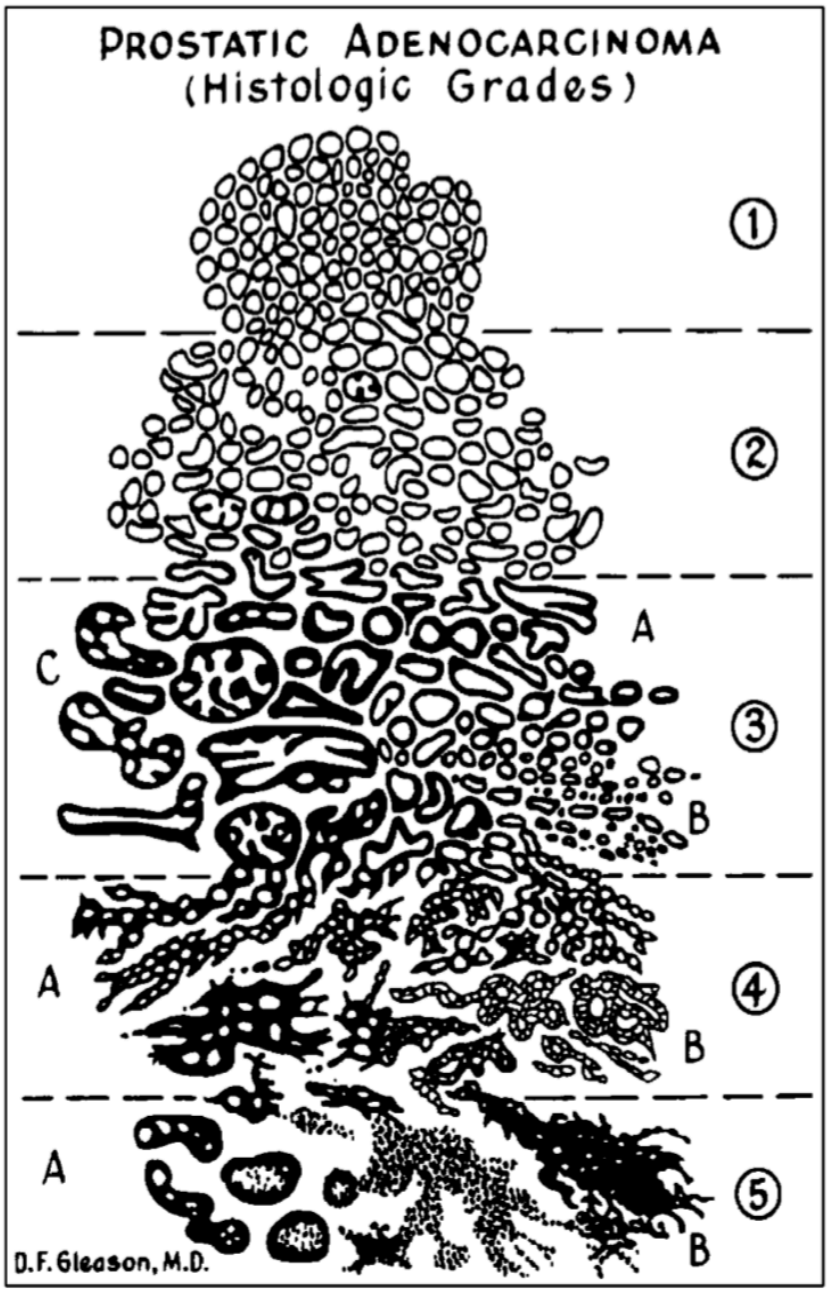

Fig. 3 *- Gleason's illustration of his grading system for prostate adenocarcinoma. Reproduced with permission from Humphrey PA, et al 2004.* [15]

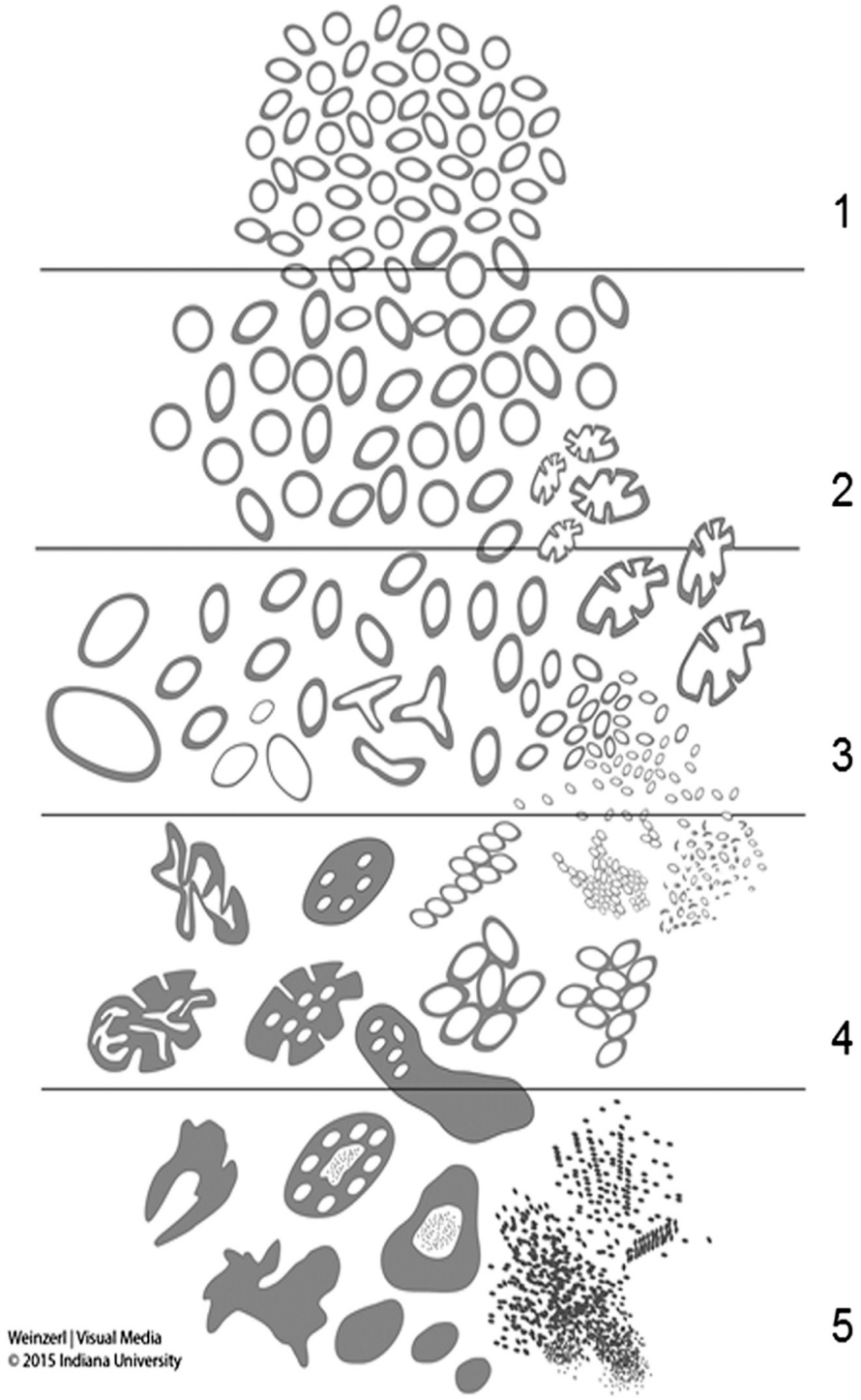

Fig. 4 *- Prostatic adenocarcinoma (histologic patterns) according to the 2015 Modified ISUP Gleason schematic diagrams. Reproduced with permission from Epstein JI, et al 2016.* [17]

Table 2 *- Histological Definition of new grading system grade.*

GGG	Histology
1	**GS ≤ 6:** *Individual well-formed glands*
2	**GS 3+4:** *Mainly well-formed glands with minor poorly- formed/fused/cribriform glands*
3	**GS 4+3:** *Largely poorly formed glands with smaller component of well-formed glands*
4	**GS 8:** *Poorly formed glands*
5	**GS 9-10:** *No gland formation and poorly formed glands*

Legend: GGG – Gleason Grade Group; GS: Gleason Score.

The second major defining factor of invasive prostatic adenocarcinoma is the loss of basal cells, as they normally lie attached to the basal membrane as described above and interpose themselves between this membrane and the luminal secreting cells. During the haematoxylin and eosin staining and fixing procedures luminal cells may be crushed making the description of the basal membrane difficult to assess. Usually, especially when confronted with small foci or low Gleason grade patterns, immunohistochemistry is used to detect with less ambiguity the absence/presence of basal cells. [16]

Nuclear and nucleolar enlargement are together the component of nuclear atypia (i.e. a large single nucleus with clearing of chromatin and an intensely pigmented big nucleolus) that make up the third criterion. [16]

1.3 Prostate cancer diagnosis

1.3.1 Digital rectal examination (DRE)

DRE is a very simple technique, mainly developed for rectal pathologies but it has become relevant also for prostate cancer due to the close contact of the prostate to the rectal wall. This diagnostic method is very simple, low cost and quick to perform but a recent systematic review and meta-analysis has found that the use of DRE alone in the primary care setting has a sensitivity and specificity below 60%, possibly due to inexperience, and can therefore not be recommended to exclude prostate cancer. [18]

1.3.2 Prostate specific antigen (PSA)

Nowadays, the most famous and used molecular biomarker used as an indicator for prostate cancer is PSA, a protease which is produced by the luminal cell and secreted into the ejaculate. Under optimal physiological condition this molecule does not cross the basement membrane but with age and in other conditions where normal histology architecture is altered (e.g., benign prostatic hyperplasia, inflammation or prostate cancer) this enzyme leaks beyond this barrier and enters the blood stream.

Although PSA increases the detection of prostate cancer up to 80% compared to the use of DRE alone [6,7], its low specificity (33%) has led in many cases to overdiagnosis and overtreatment [19] and many new genomic biomarkers from blood and urine have been developed in the last decade but none of them are currently used in routine practice in the UK. [20]

1.3.3 Transrectal ultrasound (TRUS) guided prostate biopsy

Transrectal ultrasound (TRUS) guided prostate biopsy was introduced in the late 80's [21] and 10-12 core TRUS biopsy, which is routinely done under local anaesthesia, is still the standard initial diagnostic test for patients with suspected prostate cancer in many centres worldwide. However, there are some drawbacks of this procedure, such as i) under-diagnosis of clinically significant prostate cancer; ii) over-diagnosis of clinically non-significant prostate cancer; iii) higher rates of sepsis than transperineal biopsy; iv) anterior, midline and apical tumours can be missed. [22]

This has led to two main advancements in the field: i) the transperineal approach, which has resulted in a lower sepsis rate (but a potentially higher rate of urinary retention, depending on sampling density); and ii) the use of magnetic resonance imaging (MRI)-targeted prostate biopsy that can be used as an additional test to systematic biopsy or also as a replacement test to systematic biopsy. [23]

1.3.4 MRI-targeted prostate biopsy

The main advantage of MRI-targeted biopsies is that it identifies the greatest amount of prostate cancer given the more intensive sampling of the lesion. There are three approaches to targeting biopsies to areas of interest seen on prostate MRI, each of which relies on the acquisition and reporting of a diagnostic quality MRI scan used to identify areas of interest, and the subsequent use of those diagnostic quality images in combination with real-time images of the prostate during the biopsy procedure. The three techniques are: i) visual registration of the MRI images with a real-time ultrasound image; ii) software-assisted fusion of the MRI images and the real-time ultrasound images; and iii) in-bore biopsy, which requires registration of a diagnostic quality MRI scan with a real time interventional MRI image.
Currently there is no consensus on which type of MRI- targeted biopsy performs better in a given setting, as substantial differences in methodology and reporting the findings make it difficult to reliably compare their outcomes. [24]

1.4 Prostate magnetic resonance imaging (MRI)

The purpose of this subchapter is to discuss the evolution of MRI in prostate cancer from the early 1980s to present, providing analysis of the key studies on this topic.

1.4.1 History of prostate MRI

Remarkable advances have occurred in MRI technology and image quality has dramatically improved with the introduction of high-field-strength magnets and phased-array coils. This has improved the accuracy of MRI in detecting clinically significant prostate cancer.

The timeline below (Fig. 5) outlines the major technical developments in MRI of the prostate over the last 40 years.

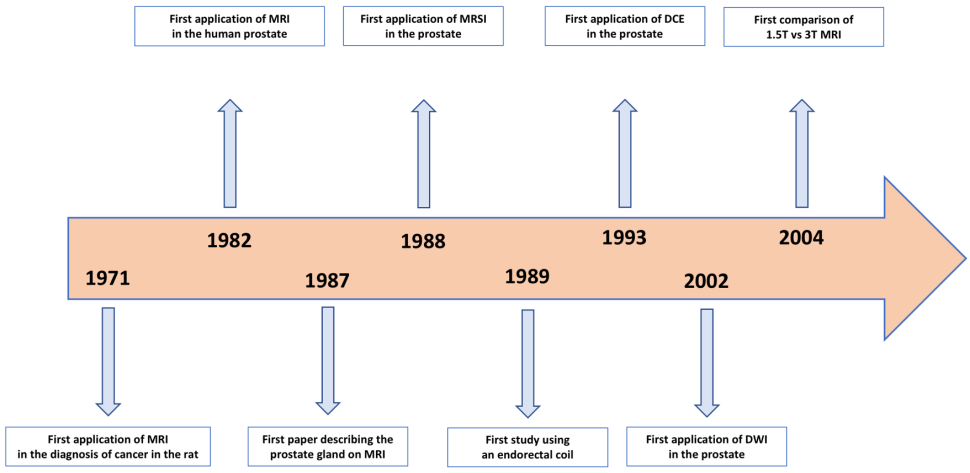

Fig. 5 *- Chronologic timeline of major technical developments in MRI of prostate. DCE = dynamic contrast enhanced. Adapted with permission from: Giganti F, Rosenkrantz AB, Villeirs G, et al. The Evolution of MRI of the Prostate: The Past, the Present, and the Future. AJR Am J Roentgenol (2019); 213(2):384-396.*

A typical multiparametric MRI (mpMRI) protocol consists of two groups of sequences:

- Morphological sequences (T1- and T2-weighted sequences)
- Functional sequences (diffusion-weighted imaging -DWI-, dynamic contrast enhanced -DCE- acquisitions, and proton spectroscopy, although the use of proton MR spectroscopy has declined).

1.4.1.1 T2-weighted imaging (T2-WI)

The first application of MRI in the diagnosis of cancer was in six normal tissue samples and two malignant solid tumours (Walker sarcoma and Novikoff hepatoma) in the rat

in 1971, where malignant tissues could be differentiated according to the different T1 and T2 relaxation when compared with the normal tissues. [25].

The first MRI study of the human prostate was performed in 1982 by Steyn and Smith on 25 men using a 0.04 T magnetic field of and a 17.53 mm slice thickness [26].

One year later, Hricak et al. [27] investigated the MR anatomy and pathological findings of the pelvis in men, including nine men with benign prostatic hyperplasia (BPH), nine with prostate cancer, and one with a lymphocele after surgery, acquiring T1- and T2-weighted spin-echo sequences in three planes (axial, sagittal, and coronal) to allow accurate volumetric assessment and to assess extension of the disease into the periprostatic adipose tissue.

In 1983, Bryan et al. [28] obtained T1- and T2-WI of four men with prostate cancer and one with BPH, and they reported that prostate cancer had an inhomogeneous appearance on MRI. However, MRI was still too expensive to be used routinely.

It was only in 1987 that Hricak and colleagues [29] published the first descriptive study of the appearance of the prostate gland and periprostatic structures on MRI. The authors discussed the technical requirements for a prostate MRI of diagnostic quality after reviewing 55 men with benign and malignant prostate and bladder disorders. They used either a 0.35- or 1.5-T system, and acquired multiplanar T1- and T2-WI with different parameters (e.g., slice thicknesses and gaps) and were able to show the anatomic structures.

1.4.1.2 Dynamic contrast enhanced (DCE) imaging

As far as DCE is concerned, Mirowitz and colleagues [30] were the first to report the impact of contrast enhancement on the staging of prostate cancer in 1993. They concluded that the use of gadolinium was not warranted for routine staging of prostate

cancer but conceded that it could be helpful in assessing seminal vesicles. Two years later, Brown et al. [31] reported the improved detection of prostate cancer after acquisition of intravenous gadolinium (0.2 mL/kg) and concluded that dynamic bolus contrast enhancement could be useful to evaluate the margins of the tumour.

After these two initial studies, the use of contrast medium in prostate MRI has seen rapid developments in data acquisition methods, with rapid series of images continuously acquired after bolus administration of contrast medium over time (i.e., with a temporal resolution that usually ranges from 5 to 15 seconds and an acquisition time that is usually ≥ two minutes). [32–34]

1.4.1.3 Diffusion-weighted imaging (DWI)

DWI shows the motion of water molecules in tissues, which is linked to tissue cellularity. Prostate cancer is characterised by greater numbers of cells and destruction of water-rich glandular tissue, resulting in a lower water diffusivity (and a lower apparent diffusion coefficient -ADC-) compared with that seen in normal tissue. A region of restricted diffusion (e.g., tumour) is hyperintense on high-*b*-value DWI and hypointense on the corresponding ADC map.

The first application of DWI for prostate cancer dates back to 2002. [35] The ADC was measured in the transition and peripheral zones of 7 healthy men and 19 men with prostate cancer. For men with prostate cancer, the ADCs were lower in the malignant tissue than non-cancerous areas (1.38 vs 1.92 × 10^{-3} mm^2/s; $p < 0.001$).

Since then, many studies and reviews have investigated the usefulness of prostate DWI, supporting its inclusion in the diagnostic pathway of prostate cancer. [36-39]

1.4.1.4 MR Spectroscopy

The first study of spectroscopic MRI of the prostate was published by Sillerud et al. in 1988. [40] However, it was only in 1995 that Kurhanewicz and colleagues [41] confirmed that citrate levels detected by spectroscopy could reliably discriminate regions of prostate cancer from healthy peripheral zone tissue and BPH, as the citrate levels were lower in patients with prostate cancer than in patients with BPH or men with normal peripheral zone prostate tissue.

Despite the initial excitement, spectroscopic MRI has now fallen out of favour for prostate cancer assessment. A multicentre study [42] showed no incremental value of spectroscopic MRI over MRI for men with relatively low-volume and low-risk disease after radical prostatectomy. However, spectroscopic MRI has proven to be a superb technique for the detection of aggressive cancers [43-45], but DWI can now give the same information in less time and with less required expertise.

1.4.2 Current role of prostate MRI

1.4.2.1 Prostate MRI acquisition

As previously mentioned, mpMRI refers to the use of different anatomical and functional imaging parameters, each of which investigates a specific aspect of the prostate gland.

1.4.2.1.1 T2-weighted imaging

T2-WI provides a highly defined anatomical image of the zonal architecture of the prostate with excellent soft tissue contrast.
In the normal prostate, the peripheral zone is characterised by hyperintense T2-signal (owing to its high glandular ductal tissue content) while the transition zone exhibits higher cellular density than the peripheral zone and appears heterogeneously hypointense. Prostate cancer is characterised by high cellularity and low water content and, therefore, returns low T2 signal but changes such as acute and chronic prostatitis, scars, irradiation, hormonal treatment effects and post-biopsy haemorrhage might mimic prostate cancer on T2-WI. (Fig. 6)

1.4.2.1.2 Diffusion-weighted imaging

As far as the current DWI protocol is concerned, a dedicated acquisition of the highest *b* values (usually 1400 s/mm^2 and 2000 s/mm^2 for 1.5-T and 3-T scanners, respectively) should be obtained. It follows that the ADC, which reflects the capability of water to move, will be lower in areas where the diffusion is restricted (e.g., prostate cancer) than in healthy tissue. (Fig. 6)

1.4.2.1.3 Dynamic contrast enhanced imaging

DCE imaging is generated by rapid acquisition of a series of T1-weighted images after intravenous injection of contrast agent (usually gadolinium)

and enables the evaluation of both the intensity and the dynamics of contrast enhancement of prostatic tissue.

Prostate cancer is characterised by early wash-in and early wash-out than non-malignant tissue, but other benign conditions (such as hyperplastic nodules and prostatitis) might have these characteristics and lead to false-positive results. [46]

The use of DCE imaging is currently debated, mainly owing to the increased costs and duration of the study, in addition to the possible side effects from the use of gadolinium (e.g. allergic reactions and accumulation in the basal ganglia) and there are data supporting the value of biparametric MRI (i.e. on the basis of only T2-WI and DWI). [47-48]

However, DCE imaging is particularly useful when T2-WI and DWI are equivocal or degraded by artefacts and in the evaluation of local recurrence after interventions that change prostate morphology. [49] (Fig. 6)

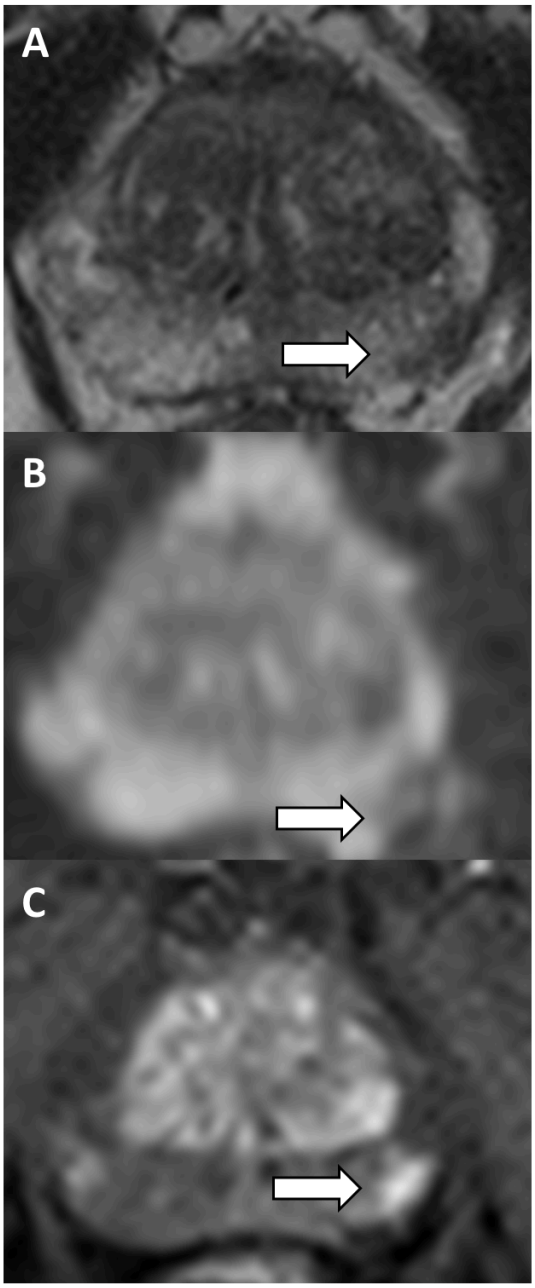

***Fig. 6**: multiparametric magnetic resonance imaging of prostate cancer in the left peripheral zone at midgland between 4 and 5 o'clock (arrows), characterised by low signal on T2-WI (A), restricted diffusion on the ADC map from DWI (B) and early enhancement on DCE (C).*

1.4.2.2 Prostate MRI interpretation

One of the most considerable challenges in prostate mpMRI has been the development of a standardized reporting system.

Dickinson and colleagues were the first to publish the results from the first international consensus meeting on prostate MRI in 2011 [50], when the use of an ordinal 5-point Likert MRI-based scale to score the likelihood of malignancy (from highly unlikely to highly likely) and a pictorial report showing lesion location were recommended. (Table 3)

Table 3 - *Likert scale for the assessment of clinically significant prostate cancer on MRI*

Likert score	Interpretation
1	Clinically significant prostate cancer is highly unlikely
2	Clinically significant prostate cancer is unlikely
3	Clinically significant prostate cancer is equivocal
4	Clinically significant prostate cancer is likely
5	Clinically significant prostate cancer is highly likely

In 2012, the European Society of Urogenital Radiology (ESUR) published the first version of the Prostate Imaging Reporting and Data System (PI-RADS) [51], which included basic recommendations for MRI acquisition, interpretation, and reporting. A PI-RADS score from 1 to 5 indicated the likelihood of a patient having clinically

significant prostate cancer on each MRI sequence (T2-WI, DWI, DCE and spectroscopy), and the overall PI-RADS score was then assessed.

PI-RADS v.2.0 and v.2.1 were subsequently released in 2015 and 2019, respectively, [52-53] following a collaborative effort of the ESUR, the American College of Radiology, and the AdMeTech Foundation.
PI-RADS v.2 simplified the interpretation of DCE-MRI and identified dominant sequences (T2-WI for the transition zone and DWI for the peripheral zone) determining the overall PI-RADS score. Moreover, spectroscopy was no longer included.
At present, PI-RADS v.2.1 is widely used in clinical practice and is very useful for less experienced radiologists who can interpret prostate MRI. However, some experienced radiologists are keener on using the subjective Likert scoring system, as they prefer scoring outside of the rigid criteria of PI-RADS taking into account other parameters (e.g., the prostate background or PSA density), given that not all situations fit the PI-RADS scoring criteria perfectly.

Future improvements will need to cover interobserver agreement, clarification and simplification of the scoring workflow and refinement of technical issues regarding mpMRI acquisition.

1.4.2.3 Prostate MRI indications

One of the main advantages of prostate MRI is its high contrast resolution (i.e., the ability to distinguish between the differences in MR signal intensity), which is

fundamental for the detection of extracapsular extension or involvement of the neurovascular bundles and seminal vesicles, along with good spatial resolution (i.e., the ability to differentiate two discrete objects).
This is the reason why mpMRI was initially used as a tool to stage patients with a diagnosis of prostate cancer prior to radical prostatectomy or radiation therapy. [49]

However, further refinements of this technique over the last decade have promoted the application of prostate mpMRI also in other settings. [49]
At present, one of the main roles of this technique is that of guiding targeted diagnostic prostate biopsies, as recently shown by different studies [54–58] (although the biopsies in the PROMIS study [56] were untargeted) that showed that mpMRI improves the yield of clinically significant prostate cancer while mitigating the overdiagnosis of clinically non-significant disease (Table 4, next page).

Table 4 *– Data from four major recent studies of MRI before first prostate biopsy. Reprinted with permission from. [54]*

Author	Country	Population	Patients (study design)	Investigator arm (n)	Comparator (n)	Threshold for MRI-targeted biopsy	Primary definition of csPCa	Men avoiding biopsy	CsPCa by MRI pathway	Detection of indolent cancer by MRI pathway	Detection of csPCa by standard TRUS biopsy	Detection of indolent cancer by standard TRUS biopsy
Ahmed et al (PROMIS) * [56]	United Kingdom	Biopsy-naïve	576 (cohort)	MRI and standard biopsy (576)	5mm template prostate mapping biopsy (576)	Likert ≥ 3	GS ≥ 4+3 or MCCL ≥ 6 mm*	158/576 (27%)	213/576 (37%)	121/576 (21%)	111/576 (19%)	90/576 (16%)
Kasivisvanathan et al. (PRECISION) [55]	Multicentre	Biopsy-naïve	500 (RCT: 252 in MRI arm, 248 in standard biopsy arm)	MRI + MRI-targeted biopsy in MRI positive (252)	10-12-core TRUS biopsy (248)	PI-RADS ≥ 3	GS ≥ 3+4	71/252 (28%)	95/252 (38%)	23/252 (9%)	64/248 (26%)	55/248 (22%)
Van der Leest et al. (4M) [58]	The Netherlands	Biopsy-naïve	626 (cohort)	MRI + MRI-targeted biopsy in MRI positive (317)	10-12-core TRUS biopsy (626)	PI-RADS ≥ 3	GS ≥ 3+4	309/626 (49%)	159/626 (25%)	88/626 (14%)	146/626 (23%)	155/626 (25%)
Rouvière et al. (MRI-FIRST) ** [57]	France	Biopsy-naïve	251 (cohort)	MRI + MRI-targeted biopsy in MRI positive (206)	10-12-core TRUS biopsy (251)	Likert ≥ 3	GS ≥ 3+4 (csPCa) **	Not specified	81/251 (32%)	14/251 (6%)	75/251 (30%)	49/251 (20%)

Legend – csPCa: clinically significant prostate cancer; GS: Gleason score; MCCL: maximum core length; MRI: magnetic resonance imaging; PCa: prostate cancer; RCT: randomised controlled trial; TRUS: transrectal ultrasound; PI-RADS: prostate imaging reporting and data system.

Note:

** in PROMIS the definition of non-significant cancer was ≤ 3mm Gleason 3 + 3, which means that non-significant cancer and clinically significant cancer does not include all cancers*

***in MRI-FIRST the definition of non-significant cancer is <6mm Gleason 3 + 3, which means that nsPCa and csPCa-A does not include all cancers*

- *PRECISION up to 4 cores per target, up to 12 per man in targeted arm*
- *4M used 2-4 cores in an in-bore MRI-targeted approach*
- *MRI-first used up to 3 targeted cores, with targeted cores being taken after standard cores.*

But prostate MRI is also useful for patients in whom the diagnosis of prostate cancer has already been established.

The benefits include:

i) providing an accurate tumour localisation for focal or radical therapy
ii) selecting appropriate candidates for inclusion and monitoring during active surveillance (discussed in the next chapter)
iii) detecting local failure after treatment.

Data from the studies above [55-58] suggest that MRI has an important role in improving the yield of clinically significant prostate cancer as well as an important role in mitigating overdiagnosis of clinically unimportant disease.

1.5 Related publications

1. Giganti F, Rosenkrantz AB, Villeirs G, et al. The Evolution of MRI of the Prostate: The Past, the Present, and the Future. AJR Am J Roentgenol (2019); 213(2):384-396.
2. Giganti F, Moore CM. MRI in early detection of prostate cancer. Curr Opin Urol (2019); 29(6):563-568

1.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study concept (publication n. 1 and 2)
- Study design (publication n. 1 and 2)
- Acquisition of data (publication n. 1 and 2)
- Interpretation of data and writing (publication n. 1 and 2)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1 and 2)

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Chapter 2 Prostate MRI and active surveillance

The findings presented in this chapter have been published in:

- *Translational Andrology and Urology* [16]

- *Archivos Espanoles de Urologia* [51]

- a book chapter (Giganti F., Stavrinides V., Moore C.M. (2018) Can MRI Replace Biopsy in Men on Surveillance? In: Klotz L. (eds) *Active Surveillance for Localized Prostate Cancer*. Current Clinical Urology. Humana Press, Cham.) edited by Laurence Klotz.

2.1 Active surveillance

The widespread use of PSA as a screening test has led to a decrease in cancer-related mortality but also to an increased detection of patients with low-risk prostate cancer at biopsy. [1]

Risk stratification for prostate cancer is based on different parameters such as clinical stage, PSA, Gleason score and an estimate of cancer volume (i.e., the number of positive cores and the maximum extent of cancer within a positive core at biopsy). [1]

In the last decade, active surveillance (AS) has been increasingly adopted as a management option in patients with low and sometimes intermediate risk prostate cancer and a life expectancy of more than 10 years. [2]

The goal of AS is to avoid treatment-related side effects whilst preserving oncological efficacy by offering appropriate treatment when there is evidence of higher risk disease. Although patients managed with AS have shown excellent outcomes, with a cancer-specific survival of 100% [3], it has been also reported in the same series that more than a third (36%) of patients on AS are likely to undergo curative intervention due to disease upgrading at subsequent biopsy or because of patient preference. [3]

2.1.1 Active surveillance protocols

At present, there is no universal consensus on the inclusion criteria for patients on AS due to the lack of prospective randomised controlled trials.

Different AS programmes [3–11] are currently being used across the world and the eligibility criteria are mainly based on PSA, DRE and TRUS-guided biopsy results, as reported in Table 5.

Table 5 *– Active surveillance protocols according to the main Institutions/Guidelines across the world.*

	Gleason Grade	Clinical stage	PSA (ng/ml)
Johns Hopkins [3]	≤ 3 + 3	≤ T1c	≤ 10
UCSF [4]	≤ 3 + 3	≤ T2	≤ 10
Royal Marsden [5]	≤ 3 + 4	≤ T2a	≤ 15
AUA [6]	≤ 3 + 3 ≤ 3 + 4	≤ T2a	10 - 20 ≤ 10
MSKCC [7]	≤ 3 + 3	≤ T2	≤ 10
PRIAS [8]	≤ 3 + 3	≤ T2	≤ 10
University of Toronto [9]	≤ 3 + 4	≤ T2b	≤ 15
UK NICE [10]	≤ 3 + 3 ≤ 3 + 4	≤ T2a ≤ T2b	< 10 10 - 20
EAU [11]	≤ 3 + 3	≤ T2a	≤ 10

Legend: PSA: prostate specific antigen; UCSF: University of California, San Francisco; AUA: American Urological Association; MSKCC: Memorial Sloan Kettering Cancer Centre; PRIAS: Prostate Cancer Research International Active Surveillance; UK NICE: United Kingdom National Institute for Health and Care Excellence; EAU: European Association of Urology. Reprinted with permission from Giganti F, Kirkham A, Allen C, Punwani S, Orczyk C, Emberton M, Moore CMM. Update on multiparametric prostate MRI during active surveillance: current and future trends and role of the PRECISE recommendations. AJR July 29, 2020. Accepted manuscript. doi:10.2214/AJR.20.23985

It is clear that there is high heterogeneity in terms of Gleason score, PSA thresholds and the definition of clinically significant prostate cancer. The commonest published criteria include Gleason score ≤ 6, clinical T1c-T2a stage, PSA < 10 ng/ml and PSA density < 0.15 ng/ml/ml.
However, some AS guidelines reported in Table 6 include also favourable Gleason 3+4 disease, even if this is still a matter of debate.

In more detail, the UK National Institute for Health and Care and Excellence (NICE) was the first national body to support AS for patients with intermediate-risk prostate cancer (i.e., PSA between 10 and 20 ng/ml, Gleason score 3+4 or clinical T2b stage) who choose not to have immediate radical treatment. [10]

In addition to this, the recent DETECTIVE consensus meeting has concluded that patients with favourable Gleason 3+4 disease (i.e., PSA < 10 ng/ml, clinical stage < T2a and a low number of positive cores) can be considered for deferred treatment. [12]

The National Comprehensive Cancer Network (NCCN) guidelines in the United States also recognise AS as an option for favourable intermediate-risk prostate cancer (i.e., organ-confined Gleason 3+4 disease, clinical T2 stage, PSA 10 -20 ng/ml and < 50% of positive biopsy cores). [13]

It should be kept in mind that patients with intermediate-risk prostate cancer are at higher risk of adverse outcomes, as it has been shown that 25% of those with intermediate-risk disease (defined as Gleason 3+4 in 1-2 biopsy cores and PSA < 20

ng/ml) on biopsy receiving immediate radical prostatectomy harbour adverse surgical pathological findings (i.e., Gleason Grade Group ≥ 3, seminal vesicle invasion or lymph node metastasis) without routine MRI. [14]

2.1.2 Re-biopsy during active surveillance

Another matter of debate is the timing, and need for re-biopsy during AS.
Although there is no universal consensus, the majority of the published AS guidelines recommend repeat surveillance TRUS-guided systematic prostate biopsy at different time points (usually every 1-3 years) and MRI with the possibility of targeting biopsies at suspicious lesions, together with periodic PSA measurements and imaging, as reported in Table 6 (next page).
In particular, in order to detect misclassification, most protocols (Table 6) still require a confirmatory biopsy and/or mpMRI within 1 year after enrolment into AS.
Progression over time and residual misclassification during follow-up are then detected by subsequent scheduled or triggered risk assessments (Table 6).

Table 6 *– Main biopsy protocols during active surveillance according to the main Institutions/Guidelines across the world.*

	Number of biopsy cores	Confirmatory biopsy	Follow-up biopsy schedule
Johns Hopkins [3]	12	1 year	Annual
UCSF [4]	12	9 - 12 months	Every 1 - 2 years
Royal Marsden [5]	10 - 12	1.5 - 2 years	Every 2 years
AUA [6]	NR	Within 24 months of diagnostic biopsy	Not specified
MSKCC [7]	10 - 12	Within 12-18 months of diagnostic biopsy	Every 2-3 years or change in DRE / PSA rise
PRIAS [8]	8 - 12	1 year	4 and 7 years
University of Toronto [9]	8 - 14	Within 12 months of diagnostic biopsy	Every 3-5 years up to age 80
UK NICE [10]	NR	If clinical or PSA changes at any time, reassess with mpMRI and/or re-biopsy.	If clinical or PSA changes at any time, reassess with mpMRI and/or re-biopsy.
EAU [11]	NR	If there is concern about clinical, mpMRI or PSA changes	If there is concern about clinical, mpMRI or PSA changes

Legend: UCSF: University of California, San Francisco; AUA: American Urological Association; MSKCC: Memorial Sloan Kettering Cancer Centrer; DRE: digital rectal examination; PSA: prostate specific antigen; PRIAS: Prostate Cancer Research International Active Surveillance; UK NICE: United Kingdom National Institute for Health and Care Excellence; EAU: European Association of Urology; mpMRI: multiparametric magnetic resonance imaging. Reprinted with permission from Giganti F, Kirkham A, Allen C, Punwani S, Orczyk C, Emberton M, Moore CMM. Update on multiparametric prostate MRI during active surveillance: current and future trends and role of the PRECISE recommendations. AJR July 29, 2020. Accepted manuscript. doi:10.2214/AJR.20.23985

2.2 Prostate MRI during active surveillance

There has been increasing interest in the use of mpMRI during AS over the last decade, and this technique has now become commonplace in AS candidates' selection due to its high negative predictive value for clinically significant prostate cancer [15]. Thus, a patient with a negative mpMRI and favourable disease on biopsy may be advised to pursue AS.

From a previous review [16] of the literature of the original articles [17-42] that investigated the role of the different MR sequences in prostate mpMRI, it has been shown that together with standard mpMRI sequences - that allow a qualitative assessment of the prostate - a quantitative approach using imaging-derived parameters such as the calculation of the ADC or texture analysis after tracing specific regions of interest around the lesions in order to get data on tissue cellularity from the images, holds promise for the detection of change in patients on AS for prostate cancer. [16]

Table 7 shows the timing of mpMRI during AS in the main guidelines:

Table 7*: Timing of mpMRI during AS in the EAU, AUA and UK NICE guidelines.*

Guidelines	MpMRI
European Association of Urology (EAU)	Before confirmatory biopsy
American Urological Association (AUA)	Can be included in the AS protocol but should be performed on a minimum 1.5T and reviewed by an experienced radiologist
UK NICE guidelines	Offer to mpMRI-naïve patients and perform at 12–18 months of AS

Legend - AS: active surveillance; NICE: National Institute for Care and Excellence; mpMRI: multiparametric magnetic resonance imaging

When looking at the table, it should be kept in mind that one of the biggest limitations lies in the conduct of mpMRI examinations, as there are still huge differences across centres in terms of MR systems (e.g., different vendors and different magnet strengths), protocol acquisition (e.g., different *b* values for DWI, controversial use of spectroscopy, different temporal resolution for DCE imaging) and inclusion criteria, making comparison across different studies challenging.

There is compelling evidence supporting the use of all sequences from mpMRI in patients suitable for AS, although we still need robust data from large studies that analyse the huge amount of quantitative data extrapolated from the different mpMRI sequences. [16]

2.2.1 Prostate MRI and biopsies in the active surveillance setting

In addition to its high negative predictive value, mpMRI during AS is very helpful in identifying patients who can benefit from additional biopsy, improving the accuracy of targeted biopsy and reducing the rate of complications. Several studies have now suggested that mpMRI can identify patients on AS in whom prostate cancer has been undersampled at initial biopsy. [15,42-43]

We know that a suspicious lesion on mpMRI is seen in two-thirds of men otherwise suitable for AS, and data from radical prostatectomies have shown that a positive mpMRI is more likely to be associated with upgrading (defined as Gleason score > 3+3) than a negative scan (43% vs 27%). [44-45]

Turkbey and colleagues reported that the incorporation of mpMRI into the D'Amico, Epstein or CAPRA scoring systems could reduce (by 85%, 75% and 91%, respectively) the number or misclassifications in assigning patients to AS or treatment using radical prostatectomy as the reference standard. [46]

By performing mpMRI before biopsy we know that MR-visible lesions with suspicious radiological features (or showing signs of radiological progression during AS) can now be targeted for biopsy, detecting a higher percentage of patients with clinically significant prostate cancer and lowering the diagnosis of clinically insignificant disease if standard biopsies are omitted. [47]

This is corroborated by the results from the multicentre ASIST trial, which initially showed no difference in the upgrade rate between standard re-biopsy or mpMRI with

two cores targeted to a lesion (i.e., Gleason Grade Group 2 upgrade: 21% vs 23%, p=0.9) during AS [48], although it should be noted that in the highly-experienced centre the upgrading rate was much higher in the MRI arm (i.e. 20% for 12-core vs 33% for MRI-targeted bx) (p=0.09). At 2-year follow up, baseline mpMRI before confirmatory biopsy resulted in 50% fewer failures of AS and less progression to higher-grade prostate cancer, confirming the value of mpMRI in the AS setting. However, significant differences (p=0.019) were observed between sites for the 98 patients in progression rate in the MRI arm, with 2/48 (4.2%) at one centre, 7/26 (27%) at another, and 4/24 (17%) at the third centre. [49]

The additional value of mpMRI and MRI-targeted biopsies to confirmatory systematic TRUS biopsies in identifying high-grade prostate cancer in patients on AS has been investigated in a systematic review in which for a total of 1,159 patients with Gleason 3+3 disease on AS based on TRUS systematic biopsy findings, 27% showed cancer upgrading (Gleason ≥3+4) using a combined approach of MRI-targeted biopsies and confirmatory systematic biopsies. Overall, 35% of patients with a positive mpMRI were upgraded, compared to 12% of patients with a negative mpMRI (relative risk 2.77). [50]

Therefore, a pre-biopsy mpMRI is strongly advised before confirmatory systematic TRUS-guided biopsies in patients on AS, together with MRI-targeted biopsies when indicated, as also confirmed by the EAU 2020 guidelines. [11]

In conclusion, there is strong evidence to support the use of mpMRI in patients with an initial biopsy suitable for AS, and to target any lesions seen on mpMRI, often in conjunction with a confirmatory systematic biopsy.

We can speculate that mpMRI may offer an opportunity to follow patients on AS without the need of performing further biopsies in the absence of signs of radiological progression, but robust data from prospective studies are still needed before widespread adoption of mpMRI as a tool to replace repeat biopsies during AS.

2.3 The UCLH pathway for MRI during active surveillance

We have seen in Tables 6 and 7 that mpMRI at the start of AS is strongly recommended by the UK NICE guidelines [10] and is also deemed suitable for repeat assessment in patients during follow-up. [51]

Table 8 (next page) shows in detail the AS protocol for low and intermediate-risk prostate cancer (i.e., PSA ≤ 20 ng/ml or Gleason score ≤ 3+4 or clinical stage ≤ T2b) recommended by the UK NICE guidelines.

Table 8 *– Active surveillance protocol according to the UK NICE guidelines. Adapted from the UK NICE guidelines (https://www.nice.org.uk/guidance/ng131).*

Timing	Tests [a]
Year 1 of active surveillance	Every 3 to 4 months: measure PSA [b] Throughout active surveillance: monitor PSA kinetics[c] At 12 months: DRE [d] At 12 to 18 months: mpMRI
Year 2 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[b] Throughout active surveillance: monitor PSA kinetics[c] Every 12 months: DRE[d]

Legend: PSA: Prostate specific antigen; DRE: digital rectal examination; mpMRI: multiparametric magnetic resonance imaging.

[a] If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy.

[b] Could be carried out in primary care if there are agreed shared-care protocols and recall systems.

[c] Could include PSA density and velocity.

[d] Should be performed by a healthcare professional with expertise and confidence in performing DRE. In a large UK trial that informed this protocol, DREs were carried out by a urologist or a nurse specialist.

At University College London Hospital (UCLH) we have a clinical image guided AS cohort that was established in 2005 in a prospective manner, as our Institution was one of the first units to use MRI in prostate cancer diagnosis.

Currently, this cohort is one of the largest of its kind in the world and includes more than 630 patients who have had a prostate mpMRI and biopsy-confirmed low to intermediate risk prostate cancer (i.e., ≤ Gleason 3+4 and PSA ≤ 20 ng/ml) as per UK NICE guidelines, and who have chosen AS as their initial management option. No maximum cancer core length or number of positive cores has been stipulated for eligibility in our cohort, due in part to the extensive use of targeted biopsies that could result in 'risk inflation' and exclude patients from AS unnecessarily. It should be also noted that the number of involved cores is not part of disqualification criteria from AS according to the recent UK NICE and European guidelines. [10,11]

The diagram in Fig. 7 indicates the mpMRI schedule undertaken based on baseline mpMRI status during AS at UCLH, with many patients having repeat MRI during AS.

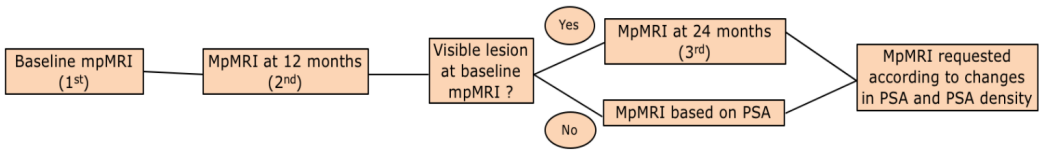

Fig. 7 *- Diagram indicating mpMRI schedule undertaken at UCLH based on baseline MRI status. Reprinted with permission from [52].*

The timing of MRI on AS is based on both baseline risk and changes during follow up. It is noteworthy that at UCLH (and in the UK to a broader extent) we have the widest use of mpMRI prior to first and confirmatory prostate biopsies during AS in the international community (80% of men in England and 41% in Wales who are referred to a specialist for suspected prostate cancer had mpMRI before biopsy according the 2019 National Prostate Cancer Audit report). [53]

The main reason lies in the collaborative working between urologists, radiologists, pathologists and radiation oncologists via multi-disciplinary team meetings that comply with national guidance as per UK NICE recommendations.

However, there are still some barriers to the adoption of an MR-based prostate cancer pathway during AS, such as the variation in both mpMRI quality and availability across the UK, and efforts to address these issues are needed.
As far as our institution is concerned, all clinical records and MR images are routinely reviewed as part of an audit performed for the internal evaluation of the AS service, including the image quality of MR scans.

2.4 Related publications

1. Giganti F, Moore CM. Magnetic resonance imaging in active surveillance - a modern approach. Transl Androl Urol (2018); 7(1):116-131.
2. Giganti F, Stabile A, Moore CM. Magnetic resonance imaging and prostate cancer: perspectives from the UK, Europe and USA. Arch Esp Urol (2019); 72(2):135-141.

2.5 Related book chapters

3. Giganti F., Stavrinides V., Moore C.M. (2018) Can MRI Replace Biopsy in Men on Surveillance? In: Klotz L. (eds) Active Surveillance for Localized Prostate Cancer. Current Clinical Urology. Humana Press, Cham. https://doi.org/10.1007/978-3-319-62710-6_11.

2.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study concept (publication n. 1, 2 and 3)
- Study design (publication n. 1, 2 and 3)
- Acquisition of data (publication n. 1 and 2)
- Statistical analysis (publication n. 1)
- Interpretation of data and writing (publication n. 1, 2 and 3)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1, 2 and 3)

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Chapter 3 The impact of 5-alpha reductase inhibitors on prostate MRI during active surveillance

In this chapter I discuss the results from a retrospective analysis that I carried out on the cohort of men who participated in the MAPPED study.

The findings from the work in this chapter have been published in *European Radiology* [9] and *Journal of Magnetic Resonance Imaging* [11].

3.1 Introduction

Dutasteride inhibits the 5-alpha-reductase enzyme, which converts testosterone to dihydrotestosterone. Dihydrotestosterone is the primary androgen found in the prostate. Differently from Finasteride (that is selective only for type 2 5-alpha-reductase), Dutasteride inhibits both type 1 and type 2 of this enzyme and is commonly used to treat lower urinary tract symptoms deriving from BPH, reducing the overall volume of the prostate. [1]

It is also known that the expression of type 1 of the 5-alpha-reductase enzyme is increased in localised and advanced prostate cancer [1], however the clinical use for Dutasteride in prostate cancer has not been licensed.

Four different published studies have investigated the impact of Dutasteride on prostate cancer in the last decade (Table 9). [2-5]

Table 9 *– Four main studies assessing the impact of Dutasteride on prostate cancer*

Study	Study name	Number of patients	Study type	Aim	Key message
Andriole et al. [2]	REDUCE	6,729	Randomised	To determine whether Dutasteride reduces the risk of incident prostate cancer, as detected on biopsy, among men who are at increased risk for the disease.	Dutasteride reduced the prevalence of prostate cancer by 24% compared to placebo over 4 years ($p < 0.001$).
Fleshner et al. [3]	REDEEM	289	Randomised	To investigate the safety and efficacy of Dutasteride on prostate cancer progression in men with low-risk disease who chose to be followed up with AS.	Fifty-five out of 144 (38%) men in the Dutasteride group were deemed to have progressed at 3 years, compared to 70/145 (48%) in the control arm ($p < 0.001$).
Schr0der et al. [4]	ARTS	294	Randomised	To assess the effect of Dutasteride on progression of PCa in patients with biochemical failure after radical therapy.	Dutasteride delayed the time to PSA doubling compared with placebo after 24 months of treatment (relative risk reduction: 66.1%) for the overall study period and significantly delayed disease progression (i.e. PSA and non-PSA-related outcomes) with an overall relative risk reduction in favour of Dutasteride of 59% ($p < 0.001$).
Klotz et al. [5]	AVIAS	80	Randomised	To study the effect of Dutasteride on the length of the off-treatment period in prostate cancer patients on intermittent androgen deprivation therapy.	No benefit from the addition of Dutasteride, with a median time off treatment for patients reaching PSA levels ≥ 5 ng/mL of 18.6 and 16.7 months for Dutasteride and placebo, respectively ($p = 0.76$).

These studies [2-5] have relied only on PSA and/or biopsy data to assess for progression, and we know that neither of these tests can accurately assess changes in tumour volume of cancer, especially while 5-alpha reductase inhibitors are taken.

However, thanks to the technical advances in prostate mpMRI, we have achieved high levels of accuracy for the calculation of imaging-based volumes of prostate cancer in men, and we can use this to assess for tumour volume change in men taking 5-alpha reductase inhibitors during AS [6,7].

3.1.1 The MAPPED study

The MRI for Primary Prostate Cancer after Exposure to Dutasteride (MAPPED) study was a prospective, double-blind, placebo-controlled trial in men with prostate cancer on AS. [6]

The primary objective of the initial study was to evaluate the effect of Dutasteride on the volume of MR detectable prostate cancer at 3 and 6 months. [6]

According to the original study protocol, published in 2013, all eligible men had to meet the 2008 UK NICE AS criteria (i.e., ≤ Gleason 3 + 4 prostate cancer and PSA ≤ 15 ng/ml) and have a measurable lesion on T2-WI. [6] All men included in the study did not have any previous prostate treatment related to prostate cancer (i.e., radiotherapy, chemotherapy, surgery, hormonal therapy, oral glucocorticoids or Gonadotropin-releasing hormone analogues) or any current/previous use of 5-alpha reductase inhibitors within the previous 12 months.

After initial assessment of suitability based on standard of care MRI, all men underwent 3T mpMRI, including Carr-Purcell-Meiboom-Gill (CPMG) sequences for

research purposes [7], which are dedicated MR sequences where T2 relaxation time for quantitative imaging are estimated by fitting an exponential curve to the signal intensities measured at multiple echo times, in order to confirm the presence of the lesion and they were then randomised to placebo or 0.5 mg of daily Dutasteride for 6 months.

MpMRI was repeated at 3 and 6 months, and each scan was reported separately by two radiologists, who were blinded to treatment allocation (Fig. 8, next page).

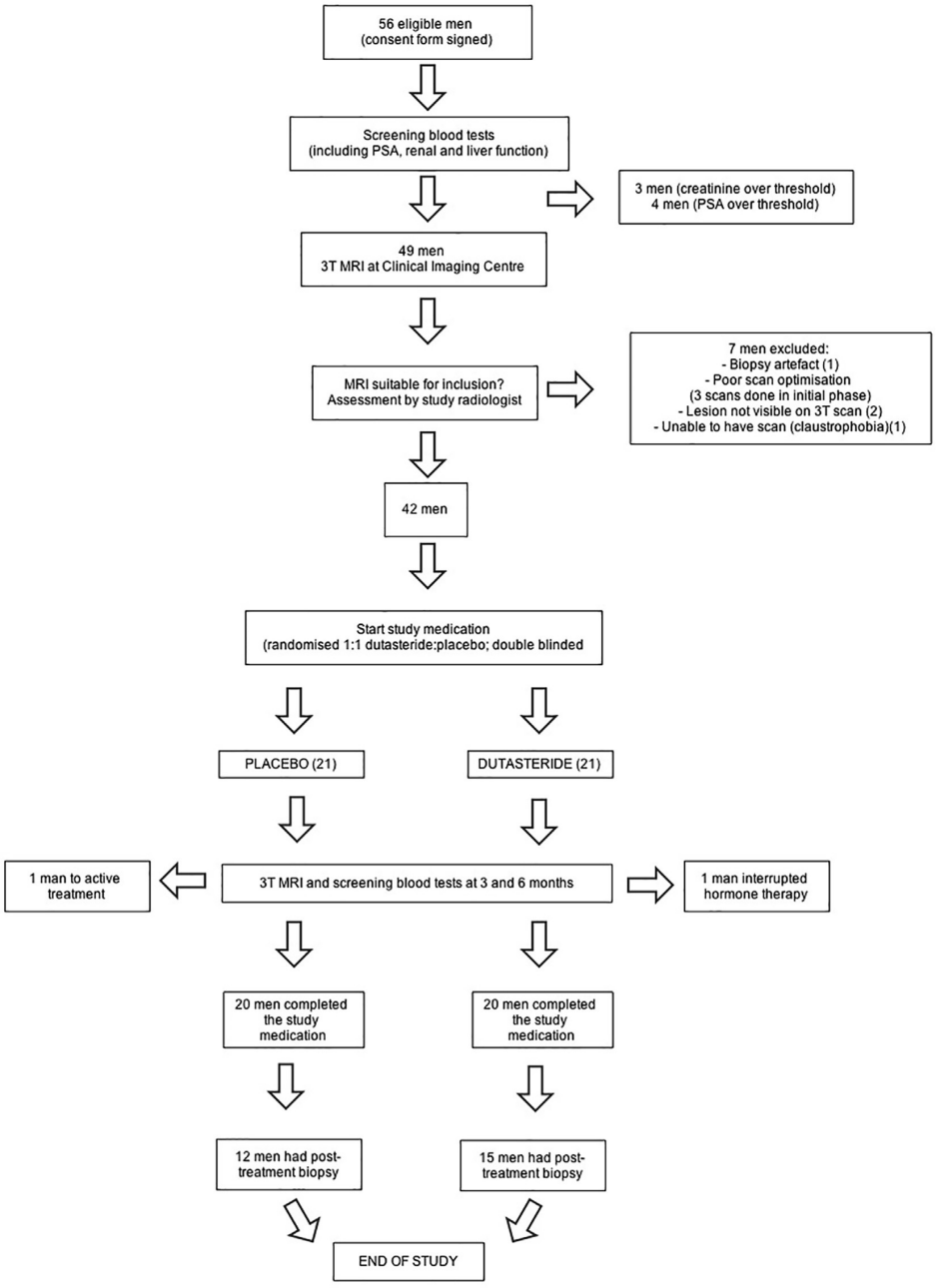

Fig. 8 *– Flowchart indicating enrolment in the MAPPED study. Reprinted with permission from [8]*

The initial results showed that the average volumes on T2-WI at baseline and 6 months were 0.55 ml and 0.38 ml in the Dutasteride group, respectively, with an average reduction of 36%. Conversely, the average volumes at baseline and 6 months on T2-WI were 0.65 and 0.76 ml in the placebo group, respectively, with an average reduction of -12% (i.e., 12% growth). The difference in percent reductions between the two groups was 48% ($p < 0.0001$). [8] The main limitation of the study was the lack of a consistent biopsy strategy at baseline, and the declining of biopsies at the end (i.e., all men were offered an end of study biopsy, but 12 of 40 declined).

Following these encouraging results, it was agreed that the initial part of this PhD would investigate two additional aspects on the impact of Dutasteride on serial imaging in men on AS for prostate cancer:

- Tumour conspicuity on DWI
- Tumour conspicuity on T2-WI

These will be now presented and discussed.

3.2 Materials and Methods

3.2.1 Dutasteride and tumour conspicuity on DWI

My research question from this ancillary study [9] was the following:

- **P**atient: In patients with low or intermediate-risk prostate cancer on AS
- **I**ntervention: does daily 0.5 mg Dutasteride
- **C**omparator: compared with placebo
- **O**utcome: affect DWI visibility between baseline and 6-month mpMRI?

A specific inclusion criterion for this retrospective analysis was the presence of a lesion scoring ≥ PI-RADS 4 at baseline mpMRI. Therefore, three men with a lesion ≤ PI-RADS 3 at baseline mpMRI were excluded from the initial population (n = 40), leaving a total of 37 men randomised to daily Dutasteride (n = 18) or placebo (n = 19).

All images were anonymised and then were assessed by me and by a senior consultant radiologist (Dr. Alex Kirkham) highly experienced in genitourinary reporting (reporting more than 3,000 prostate MR scans per year), both unaware of treatment allocation and PSA results. We used a commercial image viewing software (Osirix ® v. 4.1.2; Geneva, Switzerland).

All individual lesions were scored using the PI-RADS v.2 guidelines. [10]

The key point of this study was the assessment of the ADC values, which had been obtained tracing different regions of interest (ROIs) on the ADC maps.

As small lesions (which are a common finding during AS) are likely to include elements only partially filling the slice, a modified method for the calculation of ADC of the tumour was used in this study in order to minimise such partial volume effects. We know that the ROI analysis may not reveal the condition of the whole lesion because of the heterogeneity of lesions and because ROI only appears on one or a few lesion-containing slices. Also, drawing a volume of interest during analysis could have the potential for less operator dependence than traditional partial lesion ROI analysis, but it would be also challenging to delineate an accurate tumour margin drawing a volume of interest. In addition to this, it is necessary to combine anatomical T2-WI to evaluate the lesion because of poor anatomical details on DWI and ADC maps. Bearing in mind these aspects, we derived our method in which we used T2-WI to evaluate the anatomical details of the lesions and then we traced a smaller ROI inside the whole lesion ROI, with a diameter corresponding to half of the diameter of the greater ROI, on the ADC map and calculated the mean tumour ADC value from this area. Two additional ROIs of the same size of the whole lesion ROI (both in the non-cancerous peripheral and transitional zone in mirror position to the lesion) were contoured, as shown in Fig. 9 (next page).
The ratio between the mean ADC of the peripheral zone and that of the tumour was defined as '*conspicuity'.*

As far as the statistical analysis is concerned, continuous variables were described by means of mean and standard deviation, while categorical variables were expressed by means of frequencies and percentages. Paired T-tests were performed in the placebo and Dutasteride groups to detect significant changes in the ADC and

conspicuity between baseline and 6-month scans and also to check for differences in the size of the ROIs.

Unpaired T-tests were used to detect a difference between the mean absolute and percentage change of ADC and conspicuity between the two groups (placebo vs Dutasteride).

P values < 0.05 were considered to indicate significance.

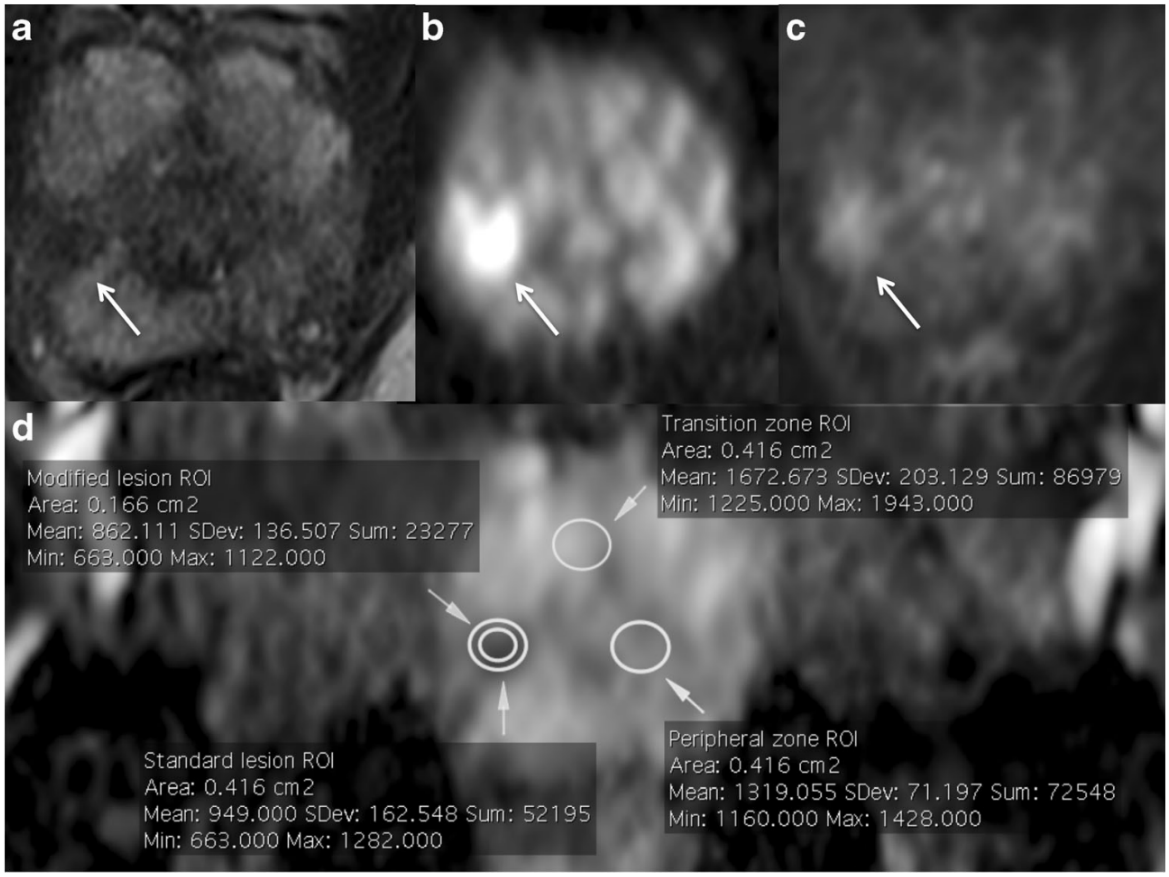

Fig. 9 *– ADC calculation according to the modified method explained in the text. The arrows show a tumour in the right mid-apex peripheral zone of the prostate on T2-weighted (a), diffusion- weighted (b) and dynamic contrast-enhanced (c) imaging, and how all regions of interest (ROIs) were positioned on the same slice of the apparent diffusion coefficient (ADC) map (d) accordingly. Reprinted with permission from [9].*

3.2.2 Dutasteride and tumour conspicuity on T2-WI

My research question from the second study [11] that originated from the MAPPED trial was the following:

- **P**atient: In patients with low or intermediate-risk prostate cancer on AS
- **I**ntervention: does daily 0.5 mg Dutasteride
- **C**omparator: compared with placebo
- **O**utcome: affect T2 relaxation time and multiecho CPMG sequences between baseline and 6-month mpMRI?

It should be stressed that during the original study specific multiecho CPMG imaging sequences [7] (which were optimised to ensure a good compromise between in-plane spatial resolution, sampling of the T2 relaxation decay, signal-to-noise ratio, and scan time) were obtained in order to extract quantitative data from T2-WI. (Fig. 10, next page)

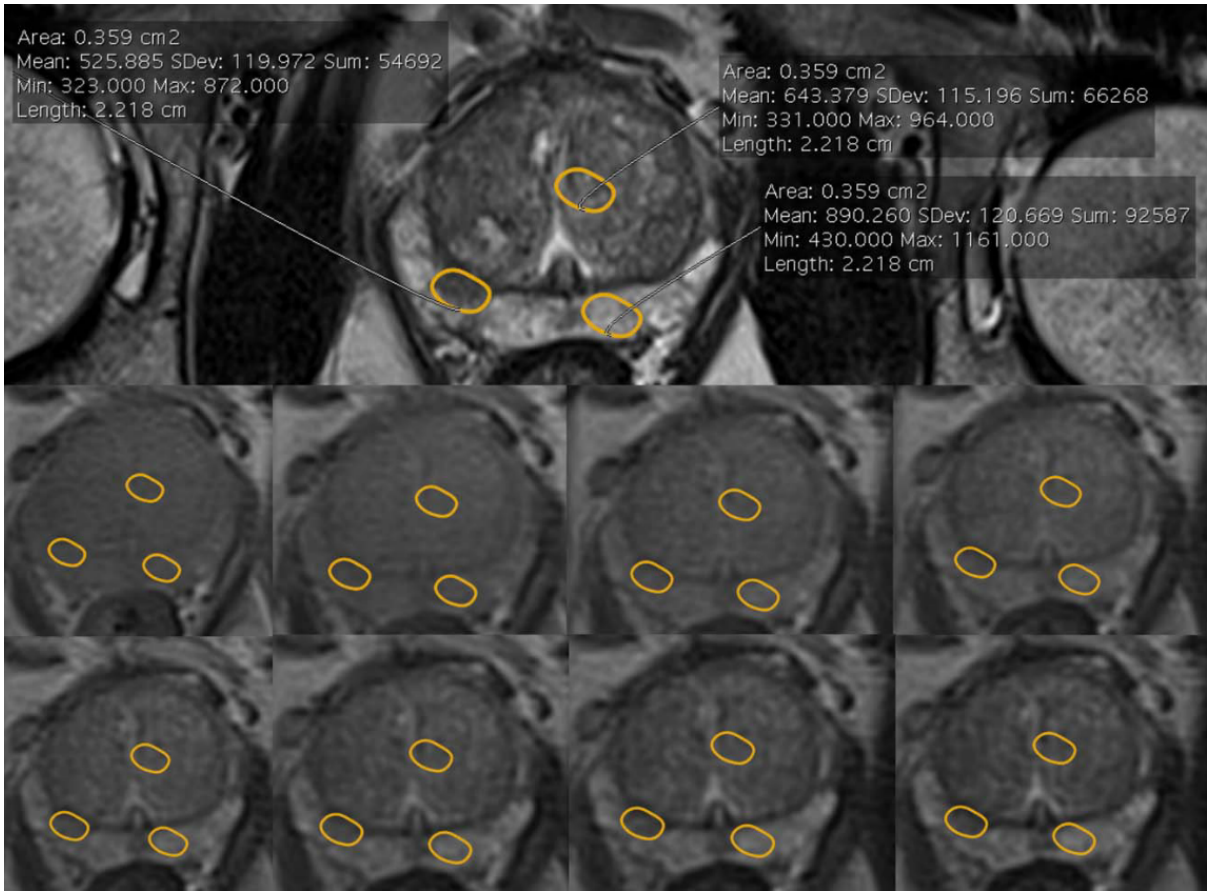

Fig. 10 *– MR images of the prostate of a 69-year-old man with a PSA of 5.83 ng/ml and a Gleason 3+4 tumour in the mid-right peripheral zone. The ROI for quantitative T2 analysis is illustrated. Three ROIs (lesion, non-cancerous peripheral, and transitional zones) were drawn on the high-resolution T2 image. These ROIs were then copied and pasted on the multiecho CPMG images (i.e., dedicated MR sequences in which T2 relaxation time for quantitative imaging was estimated by fitting an exponential curve to the signal intensities that were measured at multiple echo times). Reprinted with permission from [11].*

All lesions were visible on T2-WI at baseline and after 6 months, and image quality was adequate in all patients. All images were anonymised and then were assessed again by me and Dr. Alex Kirkham, who were unaware of treatment allocation and PSA results, using the same commercial image viewing software (Osirix ® v. 4.1.2). All scans were reported in chronological order (i.e., first baseline and then follow-up scan) using the PI-RADS v.2 guidelines. [10]

As far as the ROIs delineation in this study is concerned, we developed a novel methodology that represents a modified version of the method described in the previous paragraph [9]. More in detail, three different ROIs were drawn on the T2-WI images: i) the lesion, ii) the non-cancerous peripheral zone and iii) the non-cancerous transitional zone in mirror position to the lesion, and the signal intensity values were collected (this parameter was called '*T2-W contrast'*).

Then, the ROIs were copied on the multiecho CPMG sequences and the signal intensity of the lesion (also compared to the signal intensity of the non-cancerous tissue in the peripheral and transitional zone) was extracted; this parameter was called '*T2-Q contrast'* for each patient at baseline and after 6 months, as shown in Fig. 10. As far as the statistical analysis is concerned, continuous variables were summarised by their median values and interquartile ranges, while categorical variables were summarised by means of frequencies and percentages.

Wilcoxon signed-rank test was used to compare baseline and 6-month values, first in the placebo and then in the Dutasteride group. The Mann–Whitney U-test was then applied to investigate the differences between the two groups. The relationship between T2-W and T2-Q values was assessed by means of the Spearman's correlation coefficient.

P values < 0.05 were considered to indicate significant difference.

3.3 Results

3.3.1 Dutasteride and tumour conspicuity on DWI

Twenty one out of 37 (57%) had systematic TRUS biopsy, 5/37 (13%) transperineal template biopsy and 11/37 (30%) targeted biopsy at entry.

In terms of histology, 19/37 men (51%) had Gleason 3+3 and 18/37 (49%) Gleason 3+4 disease at entry biopsy.

A total of 35/37 (95%) regions drawn for ADC calculation were positive for the presence of cancer at entry biopsy and 28/37 (76%) lesions were also concordant at exit biopsy. Two out of 37 (5%) regions were negative at biopsy, and 7/37 (19%) men declined the exit biopsy.

There was no difference in PSA between the placebo and the Dutasteride group at baseline (6.12 ± 2.20 vs 7.14 ± 2.23 ng/mL, respectively, p = 0.168) but a significant difference in PSA between the two arms was observed after 6 months (6.72 ± 2.39 vs 4.14 ± 1.65 ng/mL, respectively, p = 0.001).

Table 10 shows mean ADC values and conspicuity from mpMRI at baseline and after 6 months. No significant differences for ADC values were observed, while a decrease in mean conspicuity was observed for men on Dutasteride (1.54 vs 1.38; p = 0.025) over 6 months.

Table 10 - *ADC, conspicuity and signal intensity values for each of the two arms included in the study at baseline and after 6 months*

	Placebo			Dutasteride		
	Baseline MRI	Follow up MRI	*p*	Baseline MRI	Follow up MRI	*p*
ADC lesion	0.99 (±0.24)	0.96 (±0.23)	0.301	1.01 (±0.15)	1.08 (±0.20)	0.069
Conspicuity	1.56 (±0.31)	1.67 (±0.34)	0.174	1.54 (±0.26)	1.38 (±0.31)	0.025
ADC TZ	1.46 (±0.18)	1.39 (±0.16)	0.061	1.32 (±0.14)	1.36 (±0.14)	0.307
ADC PZ	1.50 (±0.23)	1.55 (±0.24)	0.446	1.52 (±0.17)	1.45 (±0.21)	0.126

Legend: MRI: magnetic resonance imaging; ADC: apparent diffusion coefficient; TZ: transitional zone; PZ: peripheral zone. Reprinted with permission from [9].

Table 11 reports the difference in absolute values between the two arms over 6 months. Significant changes in absolute tumour ADC and conspicuity were observed (- 0.03 vs 0.08, p = 0.033) and (0.11 vs - 0.16, p = 0.012) in the placebo and Dutasteride group, respectively. A significant difference was also noted for ADC values in the TZ (- 0.07 vs 0.04, p = 0.039), respectively.

Table 11 *- Differences of absolute values over 6 months for ADC, conspicuity and signal intensity for each of the two arms included in the study.*

	Placebo	Dutasteride	*p*
ADC lesion	- 0.03 (±0.13)	0.08 (±0.17)	0.033
Conspicuity	0.11 (±0.33)	- 0.16 (±0.28)	0.012
ADC TZ	- 0.07 (±0.16)	0.04 (±0.16)	0.039
ADC PZ	0.05 (±0.29)	- 0.07 (±0.19)	0.132

Legend: ADC: apparent diffusion coefficient; TZ: transitional zone; PZ: peripheral zone. Reprinted with permission from [9].

Table 12 shows the comparison of the percentage changes between men taking placebo or Dutasteride. A significant increase in tumour ADC (8.56% vs - 2.27%, p = 0.048) associated with a significant decrease in conspicuity (-9.89% vs 9.25%, p = 0.013) were observed in the Dutasteride group.

Table 12 *- Differences for ADC, conspicuity and signal intensity change over 6 months (expressed as percentage) for each of the two arms included in the study*

	Placebo	Dutasteride	*p*
Δ ADC (%)	- 2.27 (±13)	8.56 (±18)	0.048
Δ Conspicuity (%)	9.25 (±26.18)	- 9.89 (±17.34)	0.013

Legend: ADC: apparent diffusion coefficient. Reprinted with permission from [9].

3.3.2 Dutasteride and tumour conspicuity on T2-WI

Twenty-two out of 40 (55%) men had Gleason score 3+3 and 18/40 (45%) had Gleason 3+4 disease at entry.

No difference in PSA was observed between the placebo and the Dutasteride group at baseline (6.2 vs. 6.4 ng/mL, $p = 0.482$), respectively while a significant difference was seen after 6 months (6.6 vs. 3.9 ng/mL, $p < 0.001$).

Table 13 compares median ROI measurements of the signal intensity on T2-WI at baseline and follow up scans. There was a significant difference between baseline and 6-month ROI areas in the Dutasteride arm (0.38 vs. 0.27 cm^2; $p = 0.005$).

Table 13 - *ROI Areas (cm^2) for each of the two arms at baseline and after 6 months*

	Placebo			Dutasteride		
	Baseline MRI	Follow up MRI	*p*	Baseline MRI	Follow up MRI	*p*
ROI (cm^2)	0.46 (0.33-0.62)	0.45 (0.33-0.64)	0.881	0.38 (0.27-0.61)	0.27 (0.20-0.53)	0.005

Legend: MRI: magnetic resonance imaging; ROI: region of interest. Reprinted with permission from [11].

Table 14 reports the comparison between T2 values of lesions and non-cancerous tissues at baseline and after 6 months. A significant difference ($p < 0.001$) between lesions and PZ for each arm at both time points was observed.

Table 14 - *T2 values (in msec) for Lesions (L) and Noncancerous Tissues (PZ and TZ) at baseline and after 6 Months for each of the two arms*

	Lesion	Non-cancerous PZ	*P (L-PZ)*	Non-cancerous TZ	*P (L-TZ)*
Placebo					
Baseline	83.5 (70.1-95.8)	133.7 (99.6-152.4)	< 0.001	97.7 (84.4-106)	0.117
6 months	81.5 (72.4-100.5)	133.7 (109.5-157.2)	< 0.001	96.2 (88.4-103.6)	0.108
Dutasteride					
Baseline	80.5 (74.2-89.5)	107.2 (97-126.6)	< 0.001	88.1 (75.4-94.6)	0.113
6 months	81.9 (72.4-85.8)	107.9 (95.9-129.5)	< 0.001	83.2 (76.5-90.2)	0.351

Table 15 reports the comparison for T2 values from all ROIs for each of the two arms, at both time points. No significant differences both for lesions and non-cancerous tissues were observed.

Table 15 - *T2 values (in msec) for each of the two arms included in the study at baseline and after 6 months*

	Placebo			Dutasteride		
	Baseline MRI	Follow up MRI	*p*	Baseline MRI	Follow up MRI	*p*
Lesion	83.5 (70.1-95.8)	81.5 (72.4-100.5)	0.179	80.5 (74.2-89.5)	81.9 (72.4-85.8)	0.681
NC PZ	133.7 (99.6-152.4)	133.7 (109.5-157.2)	0.654	107.2 (97.1-126.6)	107.9 (95.9-129.5)	0.794
NC TZ	97.7 (84.4-106)	96.2 (88.4-103.6)	0.332	88.1 (75.4-94.6)	83.2 (76.5-90.2)	0.502

Legend – MRI: magnetic resonance imaging; NC: non-cancerous; PZ: peripheral zone; TZ: transitional zone. Reprinted with permission from [11].

Fig. 11 shows no significant differences for T2W contrast at baseline and after 6 months, both in the placebo (0.40 vs. 0.43; p= 0.881) and Dutasteride arm (0.35 vs. 0.37; p= 0.668). In addition to this, no significant differences in T2W contrast between the placebo and the Dutasteride arm were observed at baseline (0.40 vs. 0.35; p = 0.409) and after 6 months (0.43 vs. 0.37; p= 0.372).

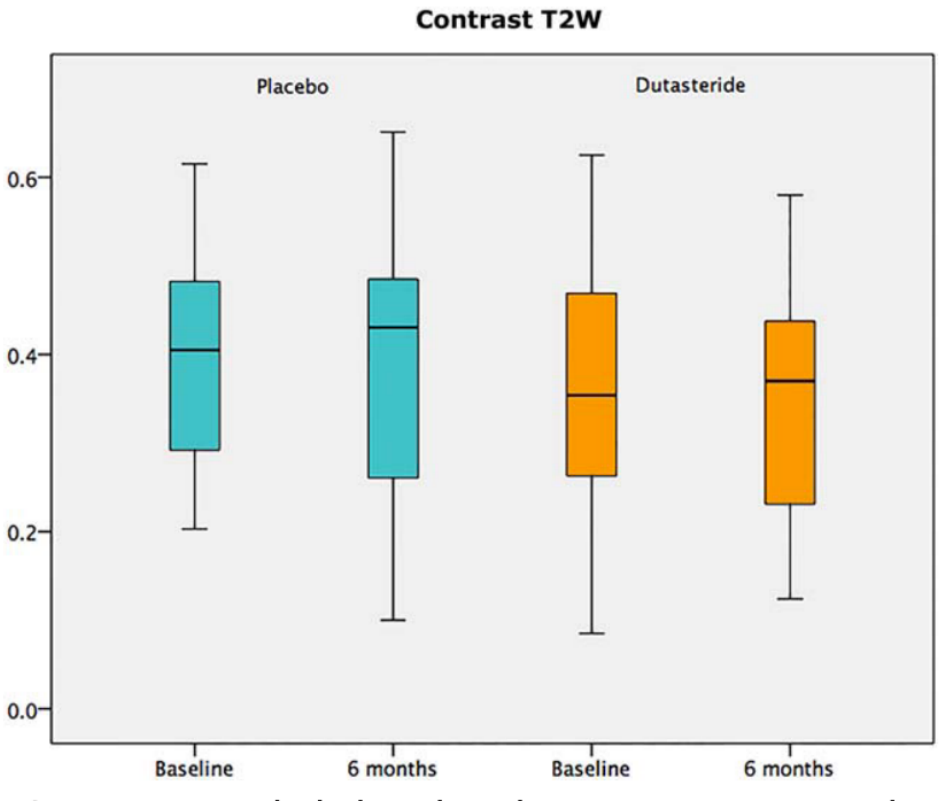

Fig. 11 *- Box-and-whisker plots showing T2-W contrast values for each arm, both at baseline and after 6 months. (Bottom of box: 25th percentile, centre line: median, top of box: 75th percentile, whiskers: 10th and 90th percentiles.) Reprinted with permission from [11].*

A significant, positive correlation between T2W and T2Q contrast values (r = 0.786; P < 0.001) was observed (Fig. 12).

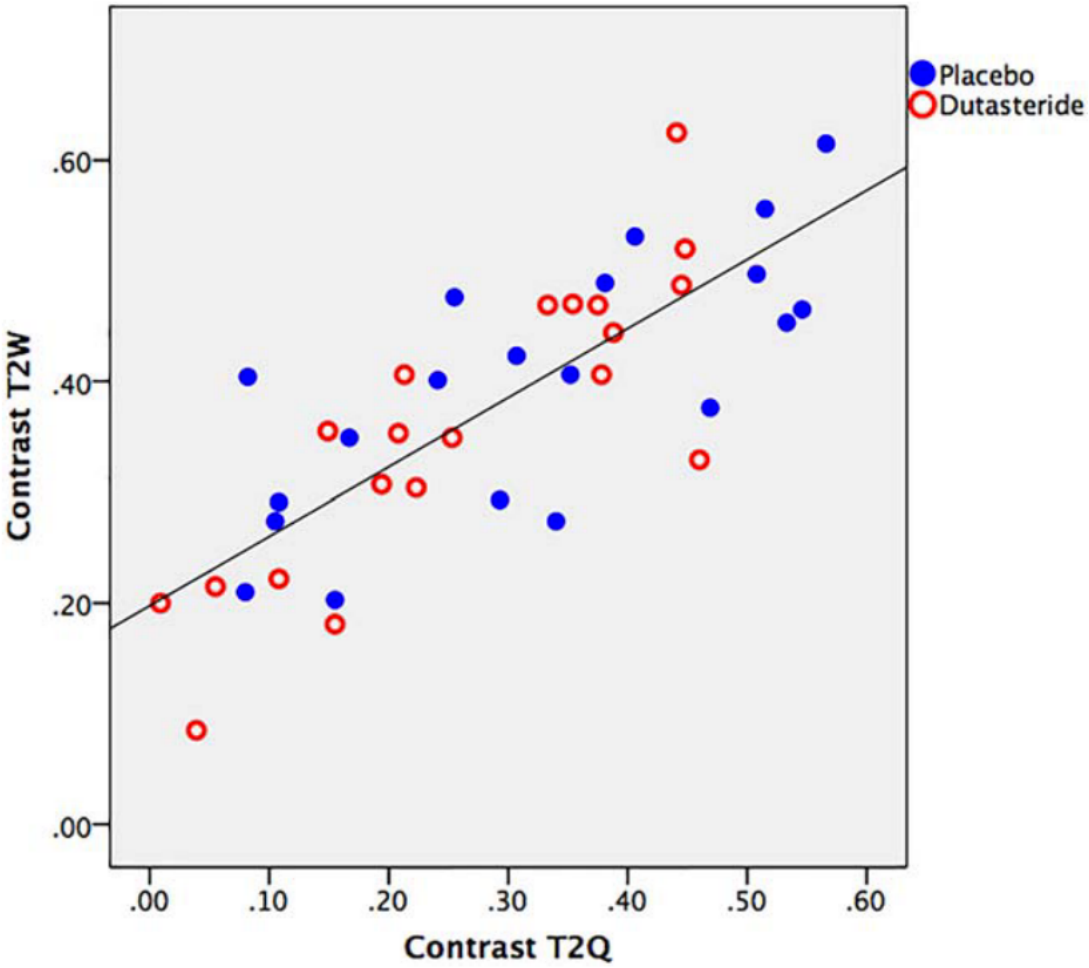

Fig. 12 - *Scatterplot of contrast from high-resolution T2-W and quantitative T2 (T2Q) imaging, showing a positive correlation (r = 0.786; p < 0.001). Reprinted with permission from [11].*

3.4 Discussion

The results presented in this chapter show the impact of daily 5-alpha reductase inhibitor (more specifically, 0.5 mg of Dutasteride) for six months on prostate MRI. In particular, Dustasteride reduces tumour conspicuity and increases the ADC values on DWI while it does not affect tumour conspicuity on T2-WI.

First of all, we know that many men on AS suffer from lower urinary tract symptoms due to benign prostatic hyperplasia, and this is commonly treated with 5-alpha reductase inhibitors, like Dutasteride. Therefore, men with low-risk prostate cancer taking Dutasteride is a common scenario in the AS setting.

The aim of this specific chapter was to assess the impact of this medication on the conspicuity of prostate cancer on mpMRI over time.
The MAPPED population represents an ideal cohort for this project, firstly because of its randomised nature (placebo vs Dutasteride) and secondly because all men enrolled in this study received both baseline and follow up MR scans.

The initial results from the MAPPED study showed that Dutasteride is associated with an average 36% reduction in prostate cancer volume compared to an average 12% increase in the placebo group at 6 months on T2-WI. [8]
The reliability of tumour volume calculations on T2-WI is corroborated by the results on T2-WI presented in this chapter, as quantitative T2 imaging also appears to be unaffected by exposure to Dutasteride, as we observed that both *T2Q contrast* and *T2W contrast* values were positively correlated. Therefore, differences in T2 values

among patients are more likely to reflect interindividual differences rather than measurement errors.
In other words, this means that the conspicuity of prostate cancer on T2-WI, which is characterised by a low T2 signal, is not affected by Dutasteride.
The clinical impact of this finding is noteworthy, as we know that visible lesions on mpMRI are more likely to progress that non-visible lesions, therefore the identification of these lesions is of utmost importance. [12]

Differently from T2-WI, the other results presented in this chapter suggest that Dutasteride significantly affects the conspicuity of a lesion on DWI and this is also linked to a significant increase in tumour ADC.

From a clinical perspective, these results are of considerable interest as they support the idea that a lower threshold for triggering biopsy could be considered for men on AS on Dutasteride (i.e., any rise in PSA on a 5-alpha reductase inhibitor should be considered suspicious and assessed accordingly), especially since small lesions and low-grade tumours (a common scenario during AS) on mpMRI could be missed. Therefore, this could adversely impact on cancer detection rates and the main recommendation following this study is that the radiologist should be always made aware if the patient is taking 5-alpha inhibitors.

From a research point of view, the strength of this work on the MAPPED population is the use of a modified method for the calculation of tumour ADC to minimise partial volume effects and obtain reliable ADC values, as the exposure to Dutasteride results into cellular involution, vacuolisation and apoptosis due to the reduction in

blood flow in both the benign and pathological prostatic tissue. [13-15] This leads to a higher diffusivity of water molecules and therefore higher ADC values on DWI, and this is why we used a ratio rather than the single ADC value from the lesion to evaluate tumour conspicuity.

There are of course limitations to the study presented in this chapter, the first being the small population. Nevertheless, it should be acknowledged that MAPPED was a prospective randomised controlled trial robust in terms of methodology and mpMRI acquisitions.

Also, the duration of the MAPPED study was relatively short (only 6 months) and therefore we cannot comment on the natural history of prostate cancer on 5-alpha reductase inhibitors on a longer period. The absence of tissue verification by radical prostatectomy could be also seen as a limitation, but it should be kept in mind that very few patients on AS (as in MAPPED) receive radical treatment if there are no signs of clinical or radiological progression.

In conclusion, the main take home messages of the two works presented in this chapter are the following:

i) Dutasteride does <u>not</u> affect tumour conspicuity on T2-WI (i.e., the accuracy of volume measurements of prostate cancer on serial T2-WI is not impaired)

ii) Dutasteride affects tumour conspicuity on DWI (i.e., the ability to monitor small lesions over time is impaired on DWI and a lower threshold for triggering biopsy might be considered)

iii) ADC is a promising quantitative imaging biomarker that reflects the effects of Dutasteride on prostate cancer at a cellular level

iv) The Radiologist should be always made aware if the patient is taking any 5-alpha reductase inhibitor

3.5 Related publications

1. Giganti F, Moore CM, Robertson NL, et al. MRI findings in men on active surveillance for prostate cancer: does dutasteride make MRI visible lesions less conspicuous? Results from a placebo-controlled, randomised clinical trial. Eur Radiol (2017); 27(11):4767-4774.

2. Giganti F, Gambarota G, Moore CM, et al. Prostate cancer detection using quantitative T2 and T2 -weighted imaging: the effects of 5-alpha-reductase inhibitors in men on active surveillance. Journal of Magnetic Resonance Imaging (2018); 47(6):1646-1653.

3.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Retrospective study concept (publication n. 1 and 2)
- Acquisition of data (publication n. 1 and 2)
- Statistical analysis (publication n. 1 and 2)
- Interpretation of data and writing (publication n. 1 and 2)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1 and 2)
- Dr Alex Kirkham (publication n. 1 and 2)
- Dr Giulio Gambarota (publication n. 1 and 2)
- The study was supported financially by GSK who also provided supplies of both drug and placebo. GSK had no input into the design, conduct and analysis of the study.

3.7 References

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[11] Giganti F, Gambarota G, Moore CM, et al. Prostate cancer detection using quantitative T2 and T2-weighted imaging: the effects of 5-alpha-reductase inhibitors in men on active surveillance. J Magn Reson Imaging (2018); 47:1646-1653.

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Chapter 4 The PRECISE recommendations

In this chapter I present the work that has led to the creation and publication of the PRECISE recommendations. I also present a dedicated PRECISE reporting tool that I have created together with an industrial partner (MIMSoftware) and that I have used for the mpMRI re-reporting during my PhD.

The findings from the work in this chapter have been published in *European Urology* [3], *Magnetic Resonance Imaging* [6] and *American Journal of Roentgenology* [7].

4.1 Introduction

In Chapter 2 we have seen that mpMRI can identify candidates for AS, who may have little benefit from therapy at entry, but still need to be monitored to allow prompt curative treatment if the disease shows signs of becoming more aggressive. [1,2]

I began this work by participating in a systematic review before the formal start of my PhD [1]. This showed that whilst there were some single-centre reports of the use of mpMRI during AS, there was no consistency in reporting the MRI data, either for an individual patient or across cohorts. In particular, whilst there had been several consensus meetings setting out acquisition and reporting standards for mpMRI in the diagnostic setting (e.g., PI-RADS), there were no clear recommendations on what constitutes a radiologically significant lesion and how radiological change is assessed on serial mpMRI during AS.

It can be challenging to determine the difference between true disease progression and variability in measurement of disease parameters during AS from a radiological point of view. Specifically, there is no agreement on how radiological thresholds for progression on mpMRI should be defined (e.g., volume, change in lesion size or appearance over time, change etc.), so that men with more aggressive and potentially lethal disease can be prompted to active treatment in a timely manner. The Response Evaluation Criteria in Solid Tumours (RECIST) criteria are deemed unsuitable for men on AS, as the current criteria use one-dimensional aspects for volume measurements and a lesion must be a minimum of 10 mm in maximal dimension before it is considered assessable. [3]

In response to this, my supervisor Professor Caroline Moore and I convened a European School of Oncology taskforce in 2016 to make recommendations on serial mpMRI reporting during AS in order to collect data across different centres in a robust and systematic manner.

The resulting publication, in which I share joint first authorship with Professor Moore, has established the guidelines for the reporting of mpMRI in AS, known as the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations, which will be discussed in this chapter. [4]

4.2 Materials and Methods

4.2.1 Establishing standards for serial mpMRI reporting during active surveillance

Researchers and clinicians with expertise in prostate mpMRI, as evidenced by published literature, were invited to participate in this project.

The final panel included 10 experts in urology, 8 in radiology, and 1 in radiation oncology (Table 16, next page) who met for a two-day face to face meeting in Milan in February 2016. Two panel members from the USA were unable to travel to the meeting and participated remotely with audio participation and desktop viewing.

For this project, the RAND Corporation and University of California, Los Angeles (RAND/UCLA) appropriateness method consensus methodology was used. [5]

Prior to the meeting, my supervisor and I drafted a set of 394 items (Table 17), which were then modified, expanded and scored for agreement by each panel member independently in the first round (i.e., prior to the face-to-face meeting).

Table 16 – *Institutions and researchers of the PRECISE working group*

Institution	Panellist(s)	Specialty
University College London Hospital, London, UK	Caroline M Moore Alex Kirkham	Urologist Radiologist
Erasmus Medical Centre, Rotterdam, The Netherlands	Ivo Schoots Chris Bangma	Radiologist Urologist
San Raffaele Scientific Institute, Milan, Italy	Alberto Briganti	Urologist
Sunnybrook Health Sciences Centre, Toronto, Canada	Masoom Haider Laurence Klotz	Radiologist Urologist
Helsinki University Central Hospital, Helsinki, Finland	Antti Ranniko	Urologist
Hôpital Universitaire Pitié-Salpêtrière, Paris, France	Raphaele Renard Penna	Radiologist
Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy	Riccardo Valdagni	Radiation Oncologist
National Cancer Institute, NIH, Bethesda, USA	Peter Pinto Baris Turkbey	Urologist Radiologist
University of California, San Francisco, USA	Peter Carroll	Urologist
Universita' Sapienza, Roma, Italy	Valeria Panebianco	Radiologist
Mount Vernon Cancer Centre, Northwood, UK	Anwar Padhani	Radiologist
Centre Hospitalier Régional Universitaire, Lille, France	Philippe Puech Adil Ouzzane	Radiologist Urologist
Memorial Sloan-Kettering Cancer Center, New York, USA	Karim Touijer	Urologist
Institut Paoli-Calmettes, Marseille, France	Jochen Walz	Urologist

Each item was scored using an ordinal 1 to 9 scale, where 1 indicated complete disagreement and 9 was the strongest agreement possible with that item for each member.

I then collated all the scores and calculated a summary of agreement, uncertainty, or disagreement (derived from the group median score) for each statement using the RAND/UCLA classical criteria that take into account the proportion of panellists scoring within a given category.

In more detail:

- a score of 1 - 3 meant that the panellist disagreed with the statement
- a score of 4 - 6 meant that the panellist was uncertain with the statement
- a score of 7 - 9 meant that the panellist agreed with the statement

For a statement to have consensus, a clear majority scoring in that category was needed.

During the second round (i.e., the two-day face to face meeting), I prepared a graphic representation of the group response, including the group median score and the degree of consensus, that was presented during the meeting. An example is given in Fig. 13.

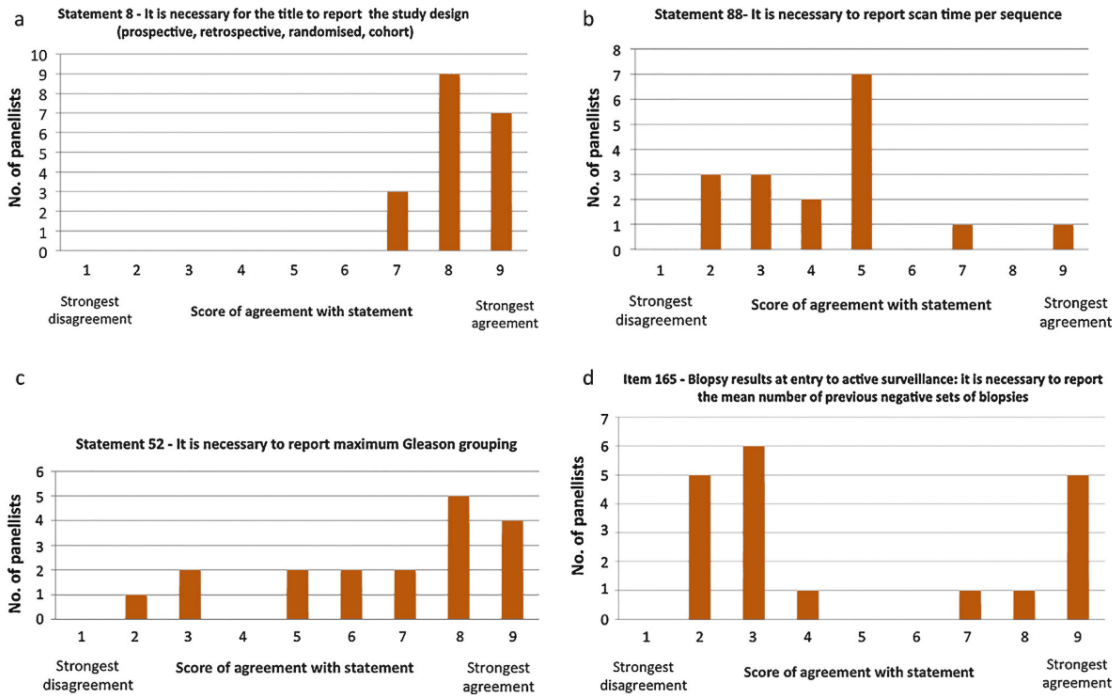

Fig. 13 *- Graphic representation of the group response for four statements showing (a) agreement and consensus (group median score: 8), (b) uncertainty and consensus (group median score: 5), (c) agreement and no consensus (group median score: 7.5), and (d) disagreement and no consensus (group median score: 3). Reprinted with permission from [4].*

This round was chaired by an independent chair who did not contribute to the scoring (Dr Peter Albertsen). Each statement was discussed individually over the course of the meeting, and some statements were modified or removed while others were added after discussion.

Each statement was then rescored anonymously by each panellist and all scores were collated, and the degree of agreement and consensus was calculated for each statement after the meeting. The items scored with the strongest consensus and the

content of the discussion were included in the PRECISE checklist of reporting criteria for studies of mpMRI in men on AS.

4.2.2 Creating a dedicated software for serial mpMRI reporting

The consensus proposed standardised reporting for mpMRI of the prostate, including accurate size measurements of each lesion over time.
This approach can be hugely time consuming for the radiologist and this is why, as part of this PhD, I have collaborated with a US-based industrial partner (MIM®) in the development of a dedicated PRECISE reporting tool. Specifically, I have worked closely with the MIM® team through web calls and virtual meetings. Thanks to my knowledge in the field, I could give them my input to improve the software and the final tool has been used to analyse the whole set of scans at UCLH.

The initial assessment of the software was done using the image database of the MAPPED population [6], which has been discussed in Chapter 3. The baseline and the 6-month mpMRI scans of 20 men (ten in the Dutasteride and ten in the placebo arm) were randomly retrieved.

I was blinded to PSA and treatment allocation and I analysed the images using two different software programmes: a widespread commercially available platform (Osirix® v. 4.1.2 - Geneva, Switzerland) and a dedicated, customised semi-automated PRECISE reporting tool (MIM® Symphony Dx v. 6.8.3 - Cleveland, OH, USA) that was specifically designed for this area.

Different parameters were assessed at each time point, including tumour volume by planimetry in all MR sequences, the ADC values and conspicuity on DWI (i.e., the mean ADC of the peripheral zone divided by the mean ADC of the tumour) using both platforms.

Reporting time for each scan using both platforms was also recorded, including the time to draw the diagram manually when Osirix® was used.

Differently from the widespread commercially available platforms, the PRECISE reporting tool provided a dedicated workflow that leaded me to report according to the PRECISE recommendations, firstly by asking to contour the prostate and any visible lesion(s) by planimetry (as shown in Fig. 15, next page) and then by manually adding clinical and imaging data (e.g. PI-RADS or Likert score, PRECISE score, parameters changed from the previous scan). [7]

A structured report that includes clinical and imaging data in line with the PRECISE case report form (shown in the Results section of this chapter) could be also generated and a comparison table between lesion characteristics at baseline and follow-up scans was included in the final report.

From a statistical point of view, data of this specific study from the MAPPED population are presented as medians and interquartile ranges and have been compared using a two-tailed Wilcoxon test.

P values have been considered to indicate a significant difference when < 0.05.

All statistical analyses have been performed by using SPSS (version 20.0; SPSS, Chicago, Illinois, USA).

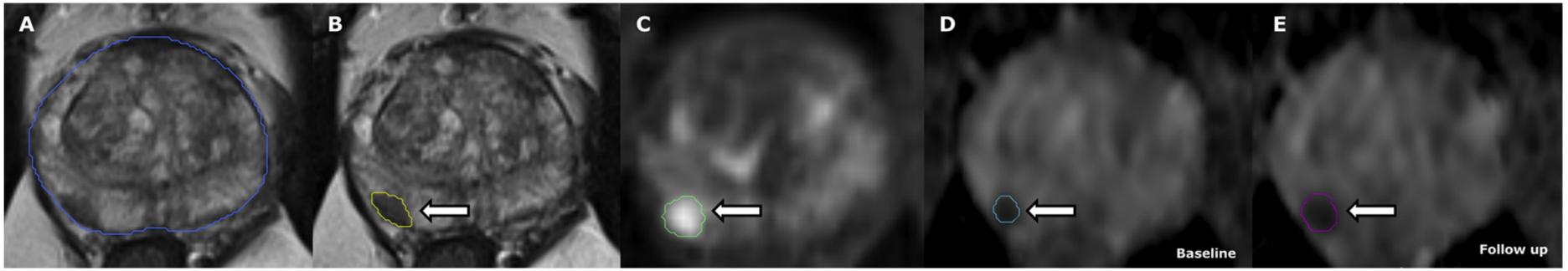

Fig. 14 *- Prostate volume (A) and lesion (B–E) contours by planimetry using the PRECISE workflow of a 59-year-old man with presenting PSA of 9.69 ng/mL and a Gleason 3+3 tumour at biopsy. This patient was in the placebo arm. The whole prostate is contoured on each slice from base to apex on axial T2-weighted sequences (A). The lesion in the right peripheral zone (arrows) is then sequentially contoured on each slice on T2-weighted (B), dynamic-contrast enhanced (C) and diffusion-weighted imaging + apparent diffusion coefficient map (D and E show the contours on the apparent diffusion coefficient map, in baseline (D) and follow-up (E) scans, respectively. Reprinted with permission from [7].*

4.3 Results

4.3.1 Establishing standards for serial mpMRI reporting during active surveillance

During the first round, 201/394 (51%) statements were scored with consensus and agreement. During the second meeting, 38 statements were deleted, 56 statements modified, and 11 statements added, giving a final set of 367 statements that were finally scored during the face-to-face meeting (Table 17).

Table 18 (next page) reports the full list of items and their scores.

Table 17 – *Summary of the group responses before and during the meeting*

	Agreement and consensus (%)	Disagreement and consensus (%)	Uncertainty or no consensus (%)
Before meeting (n=394)	201 (51)	12 (3)	181 (46)
During meeting (n=367)	144 (39)	34 (9)	189 (52)

Reprinted with permission from [4].

Table 18 – *List of items for scoring (Round 2) with corresponding level of agreement and consensus.*

Item	Disagreement with consensus	Uncertain	Agreement with consensus
TITLE and INTRODUCTION			
Section 1. Title It is necessary for the title of the study report to include the following information:			
1. Identification as a study reporting results from MRI in men on active surveillance (AS)			X
2. The use of MRI to identify men suitable for AS			X
3. The use of MRI as a surveillance tool for repeat assessment in AS			X
4. The parameters used to recommend active treatment (PSA, MRI, biopsy, patient preference)		X	
5. The "target condition" (e.g., change on MRI in men on AS; use of active treatment in men on AS; radiological progression; upgrading or upstaging)		X	
6. The population studied e.g., biopsy entry criteria, risk classification criteria		X	
7. The use of MRI targeted biopsy to identify men not suitable for AS		X	
8. The study design (prospective, retrospective, randomised, cohort)			X
Section 2: Introduction It is necessary for the introduction to report the following:			
9. A clear statement of the research question or study aim e.g., to identify parameters on baseline MRI which predict for upgrading at AS surveillance			X
10. Background information (e.g., Take up of AS amongst men diagnosed with prostate cancer deemed eligible for AS)			X
11. Any national guidelines for clinical practice (and publication date) in the country where the study was held, which need to be acknowledged (eg. UK NICE guidelines - January 2014)		X	
METHODS			
Section 3: Adherence to published AS protocol (or not) It is necessary to report the following details of the AS protocol used:			
12. Name of established protocol			X
13. Name and version of established protocol			X
14. Inclusion and exclusion criteria of protocol			X
15. Requirement for confirmatory biopsy prior to enrolment on AS			X
16. Frequency of PSA testing during protocol			X
17. Frequency of DRE during protocol		X	
18. Indication for additional biomarker tests during protocol where used (e.g., MRI for adverse PSA kinetics)			X
19. Frequency of additional biomarkers tests during protocol (e.g., PCA3)			X

20. Frequency of repeat biopsy			X
21. Trigger for repeat biopsy on protocol			X
22. Use of MRI at baseline (prior to enrolment on AS)			X
23. Use of MRI after decision to follow AS			X
24. Frequency of MRI during AS on protocol, where used			X
25. Trigger for MRI during AS (e.g., scheduled annually, above PSA threshold, prior to planned repeat biopsy)			X
26. Trigger for switch to active treatment (e.g., pathological progression, patient choice, PSA kinetics)			X
Section 4: Patient Population It is necessary to report:			
Design duration setting			
27. The setting (public hospital, academic centre, multi-centre studies)			X
28. The location of the study (city/country)			X
29. The dates between which the study recruited and followed up patients			X
30. Whether data collection was prospective or retrospective			X
31. The study design (cohort, randomised)			X
32. Whether this is an update of a previously reported cohort			X
33. When doing a multi-centre meta-analysis, the inclusion and exclusion criteria for chosen study centres and clinicians (e.g., minimum number of years of experience)		X	
34. Where relevant, details of the method of randomisation			X
35. Whether ethical permission was sought and gained			X
36. Whether recruitment was based on PSA values alone, or results from other tests such as MRI, TRUS or biopsy			X
37. If a risk classification system was used to determine eligibility			X
38. Which risk classification system was used (eg. D'Amico, Partin tables, MSKCC nomogram, ERSPC nomogram, UCSF-CAPRA score, Sunnybrook, Milan, NCCN)			X
39. A citation of the original paper stating the risk classification criteria			X
40. The parameters for risk classification should be cited individually (eg. PSA boundaries, biopsy criteria, age, MRI findings)			X
41. Whether genomic classifiers have been used in patient selection for AS		X	

42. Which genomic classifiers have been used in patient selection for AS		X	
43. Use of ultrasound findings to select men for AS		X	
Individual patient inclusion criteria			
44. Biopsy based inclusion criteria		X	
45. Maximum Gleason score			X
46. Maximum cancer core length, when available			X
47. Maximum % core involvement of cancer		X	
48. Maximum number of positive cores		X	
49. Maximum proportion of positive cores		X	
50. Maximum Gleason grouping		X	
51. Maximum PSA			X
52. Maximum PSA density		X	
53. TNM classification		X	
54. Other parameters used in inclusion criteria (eg. genomic classifiers)		X	
Section 5a: Reporting of the general conduct of the MRI It is necessary to report the following:			
55. That the MRI conduct has met the minimum criteria for prostate MRI, according to the PIRADS v 2 (ESUR & ACR) guidelines (Weinreb, European Urology, 2015)			X
56. That the MRI conduct has met the minimum criteria for prostate MRI according to other stated guidelines			X
57. Scanning angulation (axial/perpendicular to rectum)		X	
58. Total scan time		X	
59. The manufacturer, make and model of the MR machine		X	
60. The field strength of the magnet			X
61. The specific coils used (body, pelvic, phased array, endorectal, number of channels)			X
62. A brief description of the sequences used			X
63. Any adverse events from performing the diagnostic tests		X	
64. The time between most recent biopsy and MRI			X
Section 5b: Reporting of the conduct of the T2-weighted sequences It is necessary to report the following:			

65. Scanning direction (phase-encoding; anterior-posterior; right-left)	X		
66. Field of view (isotropic/non-isotropic)	X		
67. Original matrix size (128/256/512)		X	
68. Reconstruction matrix size (256/512)	X		
69. In plane resolution			X
70. Slice thickness/gaps			X
71. TE times	X		
72. TR times	X		
73. Bandwith	X		
74. NEX/averages	X		
75. Scan time per sequence	X		
Section 5c: Reporting of the conduct of the Diffusion-weighted sequences It is necessary to report the following:			
76. Special filling k-space (parallel imaging) DWI – b values used		X	
77. DWI – which image sets analysed (high b value image, ADC map, both)			X
78. The highest b value acquired			X
79. Whether the highest b value was extrapolated or not			X
80. ADC – specify whether qualitative or quantitative analysis was used		X	
81. Scan time per sequence		X	
Section 5d: Reporting of the conduct of the Dynamic contrast enhanced sequences It is necessary to report the following:			
82. DCE – temporal resolution			X
83. DCE – pharmacokinetic model used for post processing, if used		X	
84. DCE – qualitative analysis (curve types or yes/no), if used		X	
85. DCE – quantitative analysis parameters		X	
86. Scan time per sequence		X	
Section 5e: MRI reading expertise			

It is necessary to report the following:			
87. The number of radiologists reporting scans in the study			X
88. The experience of each radiologist in prostate MRI reporting		X	
89. The number of scans experience of each radiologist in prostate MRI		X	
90. Whether each scan is reported by more than one radiologist		X	
91. Where there is more than one radiologist reporting each scan, whether their reports are done separately, or in consensus			X
92. Where each radiologist reports separately how a summary value of each reported parameter Is calculated (eg. Mean absolute values; mean change)			X
93. How the variability between reporters was formally addressed		X	
Section 5f: Information available to the radiologist It is necessary to report the following patient information was made available to the radiologist reporting the scans:			
94. PSA		X	
95. Previous biopsy results		X	
96. Dates of any previous biopsies		X	
97. Digital rectal examination		X	
98. Age		X	
99. Use of anti-androgen therapies		X	
100. Use of 5-alpha reductase inhibitors		X	
101. Prior MRI scan reports		X	
102. Prior MR images			X
103. Availability of clinical information to reporting radiologist or not			X
Section 5g: Format of the radiology report It is necessary to report the following:			
104. The reporting method used (prose, scoring system, analogue scale, diagrammatic representation, MR images embedded in report)			X

105. Whether any computer aided diagnosis (CAD) software was used for MR interpretation		X	
106. The individual results of each of the MRI sequences (T1, T2, DCE, diffusion, MRS)		X	
107. The use of a visual reporting scheme, where used		X	
108. The method of visual reporting (e.g., diagrams, MR snapshots within the report)		X	
109. The use of a previously published reporting system (e.g., PI-RADS v.1 or v. 2) 1		X	
110. The sequence that most easily identifies the lesion should be identified		X	
111. The criteria giving rise to each score for each sequence should be reported in detail	X		
112. The criteria giving rise to each score for each sequence should be referenced where a previously published system is used (e.g., PI-RADS)		X	
Section 6a: Conduct of the biopsy It is necessary to report the following:			
113. The approach used for access (transrectal/transperineal/transgluteal)			X
114. The method of the target during the biopsy process (cognitive registration, image registration, in bore targeting)			X
115. Whether cores are potted separately for targeted and systematic techniques			X
116. The time interval between MRI and biopsy (median/median and range)			X
117. Any adverse events from performing the diagnostic tests		X	
118. The person(s) performing the biopsies (e.g., radiologist, urologist, technologist)		X	
119. The number of years of experience of the operator(s) in taking prostate biopsies		X	
120. The experience of the operator(s) in taking targeted biopsies		X	
121. The system used to take transperineal cores (20 zone Barzell, 12 zone Barzell, Ginsburg anterior sparing approach)		X	
122. Whether the anterior gland is routinely sampled		X	

123. Whether systematic cores are taken in all participants			X
124. The intended number of systematic cores per prostate			X
125. When targeted or systematic biopsy was done at the same biopsy session		X	
126. Whether systematic biopsy was performed blinded to MRI findings			X
127. Whether MRI targeted biopsies was performed by a different operator to the systematic biopsy		X	
For targeted biopsies, it is necessary to report the following			
128. The intended number of biopsy cores per targeted lesion			X
129. The intended sampling density per targeted lesion (cores/ml)		X	
130. The criteria for choosing a lesion to be targeted			X
131. Whether additional targeted biopsies from suspicious areas on TRUS, but not noted as suspicious on MRI, were taken		X	
Section 6b: Targeted biopsies using cognitive registration For studies involving cognitive registration, it is necessary to report the following:			
132. Whether the biopsy operator had direct access to the MR images			X
133. Which MR sequences were reviewed		X	
134. Whether the biopsy operator views a diagrammatic report		X	
135. Whether the biopsy operator views a prose report only		X	
136. Whether the biopsy operator is told distances of the target from critical structures		X	
Section 6c: Targeted biopsies using software-based image registration For studies involving software-based image registration, it is necessary to report the following:			
137. The use of rigid or dynamic registration 3			X
138. Which MRI sequence is used for the image registration		X	
139. Which software for image-registration system was used (manufacturer, make and model)			X

Section 6d: Targeted biopsies using in bore guiding equipment For studies using in bore biopsies, it is necessary to report the following:			
140. The software used (manufacturer, make and model)			X
141. The needles used (manufacturer, make and model)		X	
142. The MRI sequence used for needle placement		X	
143. The number of cores taken from each lesion			X
144. The patient position during the biopsy procedure (prone or supine)		X	
145. Whether the procedure was robot-assisted or hand assisted		X	
RESULTS			
Section 7: Baseline characteristics Baseline patient characteristics It is necessary to report the following:			
146. The age range of study participants			X
147. The race of the study participants, if available		X	
148. A flow chart of the numbers of men suitable to be considered for the study, those who were offered and accepted the study, those who were then excluded and those who completed the study			X
149. Number of men excluded from study population due to inability to have MRI (e.g., pacemaker, claustrophobia, renal impairment)		X	
150. Co-morbidity of the study participants		X	
151. Urinary symptoms of the study participants		X	
152. Sexual (dys)function of the study participants	X		
153. Number of men excluded from study population due to inability to have TRUS biopsy (e.g., not willing, too painful, infection risk, etc.)		X	
154. Number of men taking drugs, which would affect the hormonal environment in the prostate (e.g., 5 alpha reductase inhibitors or testosterone)			X
155. Number of men who have had previous surgical or minimally invasive treatment for symptomatic prostate enlargement (e.g., transurethral resection of the prostate - TURP, laser treatment)		X	

Baseline prostate characteristics It is necessary to report the following:			
156. The PSA prior to biopsy (mean/median and range)			X
157. Time between PSA and biopsy (mean/median and range)		X	
158. Digital rectal examination – DRE (positive/negative)		X	
159. Clinical T stage (T1/2/3/4)		X	
160. Radiological (MRI derived) T stage		X	
161. Prostate volume derived by ultrasound (mean/median and range)		X	
162. Prostate volume derived by MRI (mean/median and range)			X
Biopsy results at entry to active surveillance It is necessary to report the following:			
163. Mean number of previous negative sets of biopsies		X	
164. Mean number of previous positive sets of biopsies		X	
165. The number of men with each Gleason sum (e.g., 3+3, 3+4, 4+3, 4+4, etc)			X
166. The mean or median maximum cancer core length per man (including the intervening areas of benign glands)		X	
167. The mean or median maximum cancer core length per man not counting the intervening areas of benign glands (according to International Society of Urological Pathology – ISUP)		X	
168. The mean or median total percentage of biopsy material with cancer involvement		X	
169. The mean or median maximum cancer core length in mm		X	
170. Maximum Gleason score			X
171. Maximum number of positive cores		X	
172. Maximum proportion of cores, to include numerator and denominator		X	
173. Maximum mm cancer core involvement			X
174. Distribution of Gleason score			X

175. Distribution of risk category (for a named risk category)			X
Section 8: Reporting of the baseline MRI per patient It is necessary to report the following assessments for each patient:			
176. PI-RADS version 1 score (whole prostate) – if used, state which version used		X	
177. PI-RADS version 1 score (maximum for any lesion)	X		
178. PI-RADS version 2 score (whole prostate)		X	
179. PI-RADS version 2 score (maximum for any lesion)		X	
180. 1-5 scale for likelihood of clinically significant disease (whole prostate)			X
181. 1-5 scale for likelihood of clinically significant disease (maximum for any lesion)			X
182. Radiological T stage		X	
183. The appearance of the “normal” prostate (i.e., away from the area of a lesion)	X		
Using whichever scoring system has been previously identified – it is necessary to report the following:			
184. T2WI score		X	
185. DWI score		X	
186. DCE score		X	
187. MRSI score		X	
For men with a visibile lesion on MRI – it is necessary to report the following:			
188. DCE type (according to PI-RADS version 1 classification as reported in Barentsz et al. [1])	X		
189. Index lesion type (mass or diffuse change)		X	
190. Mean ADC value for the lesion		X	
191. Minimum ADC value for the lesion		X	
For each man – it is necessary to report the following volumetric assessment:			
192. Prostate size measured on T2-weighted sequences			X
193. An estimation of tumour size (e.g., by planimetry volume, derived from 3 axes, biaxial or single axis measurement)			X

194. It is not possible, based on current data, to determine the single best way to assess tumour size			X
195. The index lesion should be reported			X
196. The size of all lesions should be reported		X	
197. Index tumour size measured on T2-weighted sequences			X
198. Index tumour size measured on DCE sequences		X	
199. Index tumour size measured on high *b*-value sequences	X		
200. Index tumour size measured on ADC map	X		
201. Total tumour size measured on T2-weighted sequences		X	
202. Total tumour size measured on DCE sequences	X		
203. Total tumour size measured on high *b*-value sequences	X		
204. Total tumour size		X	
205. Volumes measured by formula (3 dimensions * 0.52)		X	
206. Lesion size for each lesion per patient (mean/median and range)		X	
207. Lesion size for the largest lesion only per patient (mean/median and range)		X	
208. Total lesion size per patient (mean/median and range) [i.e., if a patient has two lesions, the total volume for that patient would be the sum of the volume for both lesions)	X		
209. Volumes measured by planimetry (contouring on each axial slice)		X	
210. Tumour size for each set of sequences where the lesion is seen	X		
211. Tumour size for the set of sequences with greatest tumour visibility		X	
212. Tumour size for every set of sequences (where this will sometimes be “non-visible” or 0 for given set of sequences	X		
It is necessary to report the following dimensions:			

213. Longest dimension of each lesion per patient (mean/median and range)		X	
214. Longest dimension for largest lesion only per patient (mean/median and range)		X	
215. Longest dimension of lesion(s) per patient (mean/median and range) [e.g., if a patient has two lesions, the longest dimension for that patient would be the sum of longest dimension of both lesions)	X		
216. Maximal diameter of lesion in axial plane		X	
217. Two dimensions (right-angled) including the longest dimension for each lesion (mean/median and range)		X	
218. Two dimensions (right-angled) including the longest dimension for the largest lesion		X	
219. Longest dimension for the index lesion (mean/median and range)			X
220. Two dimensions (right-angled) including the longest dimension for the index lesion (mean/median and range)		X	
It is necessary to report the following index of suspicion:			
221. Likelihood of clinically significant cancer (Likert 1-5, PI-RADS 1-5) per lesion			X
222. Likelihood of extraprostatic extension per lesion (Likert 1-5 or yes/no/maybe)			X
223. Likelihood of seminal vesicle involvement (Likert 1-5 or yes/no/maybe)			X
224. Likert value (1-5) for suspicion of T3 disease per lesion		X	
225. Overall likelihood of clinically significant cancer (per prostate, Likert 1-5)			X
226. Overall PI-RADS v. 1 score for the whole prostate		X	
Section 9: Reporting of the follow-up MRI per patient It is necessary to report the following assessments for each patient:			
227. The same criteria used at baseline need to be assessed also at follow up			X
The reporting of a change on prostate MRI at follow up compared to baseline For an individual patient it is necessary to report the following parameters of likelihood of significant change:			
228. A Likert score (1-5) for likelihood of significant change			X

229. A Likert score (1-5) of likelihood of change, with an explanation of the reason for that likelihood given			X
230. A Likert score (1-5) of likelihood of significant change based on: - disease abnormality disappeared/normal appearance - improving disease: morphology and/or function - stable cancer abnormality (morphology/function) and/or no new focal/diffuse lesion consistent with cancer - worsening disease state: morphology and/or function - new abnormality consistent with disease worsening		X	
For an individual patient it is necessary to report the following parameters of change of lesion volume:			
231. % change in size of each lesion from previous scan to latest scan		X	
232. % change in size of each lesion from baseline scan to latest scan		X	
233. > 20% change in size	X		
234. > 30% change in size	X		
235. > 50% change in size		X	
236. 100% (doubling) of lesion size		X	
237. Lesion becoming non-visible on follow up			X
238. Absolute values of lesion size at baseline and latest scan			X
239. Absolute values of lesion size at current and previous scan			X
240. Absolute values of lesion size at each scan			X
For an individual patient it is necessary to report the following parameters of change of lesion diameter:			
241. Absolute values for lesion diameter at baseline and latest scan		X	
242. Absolute values for lesion diameter at current and previous scan		X	
243. Absolute values of lesion volume at each scan		X	
244. > 20% change in diameter	X		
245. > 30% change in diameter		X	
246. > 50% change in diameter		X	

247. 100 % (doubling) of lesion diameter		X	
For an individual patient it is necessary to report the following parameters of change:			
248. Change in the “normal” gland (i.e., away from a given lesion)		X	
249. Appearance of any new lesion			X
250. Appearance of any new lesion of volume > 0.2 cc (6 mm diameter)		X	
251. Appearance of any new lesion of volume > 0.5 cc (10 mm diameter)		X	
252. Appearance of any new lesion of volume > 1 cc (12 mm diameter)		X	
253. Any change in PI-RADS score on most recent scan			X
254. Any change in Likert score of clinical suspicion of significant cancer on most recent scan			X
255. The visibility of a lesion on an additional sequence compared to the visibility of the lesion at baseline		X	
256. Either quantitative or qualitative analysis of ADC values		X	
257. A change in the quantitative DCE analysis (e.g., from type 2 to type 3)	X		
258. A change in the qualitative DCE analysis		X	
259. An increase in conspicuity on any sequence		X	
260. An increase in suspicion of disease requiring treatment based on abutment/bulging/extension to/through the capsule (radiologic T stage progression)		X	
261. An increase in suspicion based on the extension into seminal vesicles (radiological T-stage progression)			X
262. An increase in suspicion based on the appearance of a suspicious lymph node (radiological N-stage progression)			X
263. An increase in suspicion based on the appearance of a bone lesion (radiological M-stage progression)			X
For a cohort of men with baseline and follow up MR imaging, it is necessary to report:			
264. Mean change in index lesion size over time		X	
265. Mean change in total tumour size over time		X	

266. The proportion of men exceeding a given threshold of change (i.e., < 20% increase)		X	
267. The proportion of men who have lesions that exceed a given size thresholds (e.g., > 0.5 mls - > 8 mm diameter)		X	
268. Different outcomes depending on baseline lesion size (e.g., > 2 mm change in absolute diameter for lesions < 8 mm, > 20 % increase in size for lesions > 8 mm diameter)		X	
269. A waterfall plot showing lesion change over time across the cohort		X	
Section 10: Reporting of the follow-up biopsy results per patient It is necessary to report the following:			
270. The mean/median number of cores per prostate			X
271. Separate reporting of systematic and targeted cores			X
272. Reporting according to location or zone of origin using a diagram		X	
273. Location or zone of origin using a standardised reporting scheme (e.g., peripheral cores, anterior cores, etc.)		X	
For targeted biopsies, it is necessary to report the following:			
274. The mean/median number of lesions per patient from which at least 1 targeted core was taken			X
275. The total number of lesions in the population from which at least 1 targeted core was taken			X
276. The mean/median number of cores per lesion			X
277. The mean/median number of cores per prostate			X
278. The number of men in each Gleason group (1= 3+3; 2=3+4; 3= 4+3; 4=4+4; etc.)			X
279. The mean/median maximum cancer core length per patient using targeted cores alone			X
280. The mean/median total cancer core length per patient using targeted cores alone		X	
281. The mean/median percentage cancer core length per patient using targeted cores alone		X	
282. The number of men in each Gleason grouping using systematic cores alone			X

283. The mean/median maximum cancer core length per patient using systematic cores alone			X
284. The mean/median total cancer core length per patient using systematic cores		X	
285. The mean/median percentage cancer core length per patient using systematic cores alone		X	
286. The maximum cancer core length and Gleason grouping per patient, irrespective of whether this was derived from systematic or targeted cores			X
Section 11: Reporting of additional measures per patient It is necessary to report the following:			
287. Use of genomic classifiers (serum based)		X	
288. Use of genomic classifiers (tissue based)		X	
289. Use of genomic classifiers (urine based)		X	
290. Use of nomogram scores for likelihood of significant disease		X	
291. Use of nomogram scores for likelihood of disease progression		X	
Defining AS outcomes Section 12a: Reporting non-radiological parameters to allow assessment of disease progression Change in the following parameters should be reported and included in the definition of significant change in men on AS for prostate cancer:			
292. Gleason grading			X
293. Gleason grouping			X
294. Maximum cancer core length in mm (counting the intervening areas of benign tissue)			X
295. Maximum cancer core length in mm (not counting the intervening areas of benign gland, according to the method recommended by ISUP)		X	
296. Total cancer core length in mm		X	
297. DRE findings		X	
298. PSA			X
299. PSA density			X
300. PSA velocity		X	
301. PSA doubling time			X

Section 12b: Thresholds for recommending active treatment based on systematic biopsy alone On a per patient level the following finding in at least one biopsy core of at least the following histological grade or core length confers clinically significant prostate cancer:			
302. Gleason 3+4		X	
303. Gleason 4+3			X
304. Gleason 7		X	
305. Gleason ≥ 8			X
306. MCCL > 2 mm and/or Gleason ≥ 3+4 (Goto criteria)	X		
307. MCCL ≥ 3 mm and/or Gleason ≥ 3+4 (Harnden criteria)	X		
308. MCCL ≥ 4 mm and/or Gleason ≥ 3+4 (UCL definition 2)		X	
309. MCCL ≥ 5 mm and/or Gleason ≥ 3+4 (Haffner criteria)		X	
310. MCCL ≥ 6 mm and/or Gleason ≥ 4+3 (UCL definition 1)			X
311. MCCL ≥ 6 mm and/or Gleason 3+4		X	
Section 12c: Defining outcome – recommending active treatment according to a composite risk assessment On a per patient level the following criteria confer a threshold, which should trigger active treatment in men on AS:			
312. D'Amico intermediate risk (T2b, Gleason 7, PSA > 10 ng/ml or PSA density < 0.2 ng/ml		X	
313. D'Amico high risk (T2c, Gleason score ≥ 8, PSA > 20 ng/ml or PSA density > 0.2 ng/ml			X
314. Stage T1b/N0/M0	X		
315. Stage T2a/N0/M0	X		
316. Stage T2b/N0/M0		X	
317. Stage T3b/N0/M0			X
318. Any N1			X
319. Any M1			X
Section 12d: Defining outcome – MRI based definitions of radiological progression			
320. Any increase in tumour volume on any MRI parameter, which has been repeated after baseline		X	

321. There are insufficient data at present to define radiological progression in men on active surveillance for prostate cancer			X
322. A 20% increase in tumour volume on any MRI parameter, which has been repeated after baseline		X	
323. A 50% increase in tumour volume on any MRI parameter, which has been repeated after baseline		X	
324. A 100% increase (i.e., doubling) in tumour volume on any MRI parameter, which has been repeated after baseline		X	
325. Any increase in largest tumour diameter on any MRI parameter, which has been repeated after baseline		X	
326. A 20% increase in largest tumour diameter on any MRI parameter, which has been repeated after baseline		X	
327. A 50% increase in largest tumour diameter on any MRI parameter, which has been repeated after baseline		X	
328. A 100% increase (i.e., doubling) in largest tumour diameter on any MRI parameter, which has been repeated after baseline		X	
329. An increase in conspicuity from baseline to repeat MRI on T2-weighted MRI		X	
330. An increase in conspicuity from baseline to repeat MRI on dynamic contrast enhanced (DCE) images		X	
331. An increase in conspicuity from baseline to repeat MRI on diffusion weighted images (highest *b*-value)		X	
332. An increase in conspicuity from baseline to repeat MRI on diffusion weighted images (ADC values)		X	
333. Appearance of a new lesion on MRI		X	
334. Change in characteristics of a lesion on MRI (e.g., visibility on diffusion and T2-WI compared to visibility on T2-WI alone)		X	
335. Change in radiological T-stage to > T3a			X
The following actions should be recommended for clinically significant change on MRI:			
336. Repeat MRI after a given interval		X	
337. Additional imaging (e.g., PET-CT)	X		
338. Repeat standard biopsy		X	
339. Repeat standard and targeted biopsy		X	

340. Targeted biopsy to suspicious area		X	
341. Discussion of active treatment		X	
342. Recommendation for active treatment	X		
343. There is too little publicly available data to make recommendations for action based on change on MRI			X
Section 13: Statistical analysis Power and sample size analysis – where possible, it is necessary to report the following:			
344. All numerators and denominators should be apparent in either the text or table for all percentages			X
345. Where a scan has been reported by more than one radiologist, the effect of inter-reader variability on the responses			X
346. Whether any effect is dependent on the size of the baseline lesion			X
347. Whether outliers (e.g., very large or very small lesions) were excluded			X
348. How the disappearance of lesions is handled in the statistical analysis			X
In order to be able to assess the added value of a single reporting item - in addition to baseline clinical data - it is important to assess and report the following:			
349. Univariate analysis			X
350. Multivariate analysis			X
351. Odds ratio for a single unfavourable factor			X
352. Odds ratio for a combination of unfavourable factors			X
When choosing a single reporting parameter to add value to the baseline clinical assessment, it is important to assess:			
353. PI-RADS v. 1 score		X	
354. PI-RADS v. 2 score			X
355. A 1-5 score of likelihood of clinically significant disease		X	
356. Minimum ADC value of lesion	X		
357. Mean ADC value of lesion		X	
358. Index lesion type (mass/no mass)		X	
359. Index lesion volume		X	

360. Index lesion maximal diameter		X	
When choosing a single imaging feature to add value to baseline clinical assessment, the most important imaging sequence is:			
361. T2-WI		X	
362. DCE	X		
363. ADC		X	
364. DWI (high *b*-value)		X	
365. MRSI	X		
DISCUSSION			
Section 14: Discussion It is necessary for the following to be reported:			
366. The clinical applicability of the study findings			X
367. The correlation of observed MRI changes to traditional tools to monitor disease significance during active surveillance (DRE, PSA kinetics, biopsy findings)			X

(1) Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22(4):746-57

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4.3.1.1 The PRECISE checklist

All statements included in the PRECISE checklist (Table 19) were scored with consensus and agreement and outline the key recommendations for reporting a cohort of men receiving serial mpMRI during AS.

Table 19 *– The PRECISE checklist*

Item	Section of paper	Description
1	Title	The study should be identified as reporting results from MRI in men on active surveillance, either to identify men as suitable for AS or as a tool for repeat assessment on AS.
2	Introduction	The introduction should include a clear statement of the research question or study aim (e.g., correlation of pathologic outcomes with radiologic change, assessment of radiologic change on repeat MRI) and background information such as the take up of AS in men deemed suitable.
3	Study design and population	The setting, location, and recruitment period and study design (prospective/retrospective) should be reported. It should be made clear (and citation given) if the report is an update of a previously published cohort. The inclusion and exclusion criteria with the maximum Gleason score, maximum PSA, and the name, version, and citation of an established AS protocol or risk classification system (where relevant) should be reported. The requirement for confirmatory biopsy, frequency of PSA testing, and the indication and frequency for biopsy, MRI, and any additional test (eg, genomic classifiers). Indications for a switch to active treatment should be specified.

4	Conduct of the MRI	Whether or not the MRI conduct met the minimum criteria set by the European Society of Uroradiology and the American College of Radiologists or other stated guidelines. The field strength and the specific coils used should be stated including a brief description of the sequences. The in-plane resolution and slice thickness of the T2W images should be stated; the image sets analysed for DWI including the highest b-value acquired and whether the highest b-value was extrapolated or not; the temporal resolution for DCE images.
5	Reporting of the MRI	The number of radiologists reporting scans in the study should be stated. The availability (or not) of clinical information and previous MRI images to the reporting radiologist should be stated. When more than one radiologist reports a scan, it should be stated whether this is done separately or in consensus. When done separately it should be stated how a summary value was derived (e.g., mean absolute values or mean change between scans per reporter). The reporting method used (e.g., prose vs diagrammatic report, name and version of scoring system) should be given.
6		The anatomic approach (transrectal/transperineal) and method of targeting MRI lesions; the use of separate pots for targeted and systematic cores (if applicable). The time interval between MRI and biopsy (median and range). Whether systematic cores are taken in all, and the intended number of systematic cores per prostate and targeted cores per lesion; whether systematic biopsy was performed blind to MRI findings. The criteria for choosing a lesion to be targeted, whether the biopsy

		operator had direct access to the MR images. Where software assistance was used for registration of MRI and ultrasound images, the manufacturer and model should be stated.
7	Patient characteristics	The age range, baseline PSA, and MRI-derived prostate volume, distribution of Gleason score, and risk categories across the group and the MCCL. The number of men taking drugs that would affect the hormonal environment of the prostate (e.g., 5a-reductase inhibitors, testosterone) should be recorded. A flowchart of participants showing numbers of men eligible, offered and enrolled in the study, with those who continue on AS and the treatment status of those who are not on AS.
8	Individual patient baseline MRI report	The baseline MRI report should contain the prostate volume measured on T2-WI and a likelihood of clinically significant cancer on a scale of 1–5 for the whole prostate and for each lesion. The likelihood of extraprostatic extension and seminal vesicle involvement should be reported on a 1–5 scale. The index lesion size should be reported using volume (by planimetry or derived from three diameters) or measurement of 1 or 2 diameters.
9	Follow-up MRI	In addition to features reported at baseline, any subsequent MRI report should include the following: • A score on a 1–5 scale for the likelihood of significant change, along with a description of the change that has given rise to the score (e.g., change in size, change

		in conspicuity on one or more sequences) • Any change in likelihood of significant cancer (1–5 scale) • An increase in suspicion due to extension into seminal vesicles or a suspicious lymph node or bone lesion • Absolute values of lesion size at baseline and each subsequent scan • The appearance of any new lesion Any lesion becoming nonvisible.
10	Reporting of follow-up biopsy	Separate reporting of systematic and targeted cores with a MCCL and Gleason grouping per patient irrespective of whether this was derived from targeted or systematic cores; mean/median number of cores per prostate and per lesion; mean/median number findings of lesions per patient where targeted cores were taken.
11	Statistical analysis	The effect of inter-reader variability; whether any effect depends on the size of the baseline lesion; whether outliers (very large or very small lesions) were excluded; how the disappearance of a lesion is handled in the statistical analysis. Where there is adequate power to do so, univariate and multivariate analysis should be used to assess the added value of a reporting statement to baseline clinical data; the odds ratio for a single and a combination of unfavourable factors should be given.
12	Discussion	The clinical applicability of the findings should be discussed, along with the correlation of the observed MRI changes with traditional tools to measure disease progression (DRE, PSA kinetics, biopsy findings)

Legend - AS = active surveillance; DCE = dynamic contrast-enhanced; DRE = digital rectal examination; DWI = diffusion-weighted imaging; MCCL = maximum cancer core length; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; T2W = T2-weighted. Reprinted with permission from [4].

4.3.1.2 The PRECISE score

In addition to this, a 1-to-5 Likert scale (i.e., the PRECISE score) for the reporting of the likelihood of radiological progression was created (Table 20). The PRECISE score estimates the likelihood of radiological progression during AS on serial mpMRI. A PRECISE score of 1 or 2 denotes radiological regression, a PRECISE score of 3 indicates stability and PRECISE score of 4 or 5 implies progression. [8]

Table 20 *- Assessment of likelihood of radiological progression on MRI in patients on active surveillance (PRECISE score)*

PRECISE score	Assessment of likelihood of radiological progression	Example
1	Resolution of previous features suspicious on MRI	Previously enhancing area no longer enhances
2	Reduction in volume and/or conspicuity of previous features suspicious on MRI	Reduction in size of previously seen lesion that remains suspicious for clinically significant disease
3	Stable MRI appearance: no new focal/diffuse lesions	Either no suspicious features or all lesions stable in size and appearance
4	Significant increase in size and/or conspicuity of features suspicious for prostate cancer	Lesion becomes visible on diffusion-weighted imaging; significant increase in size of previously seen lesion
5	Definitive radiologic stage progression	Appearance of extracapsular extension, seminal vesicle involvement, lymph node involvement, or bone metastasis

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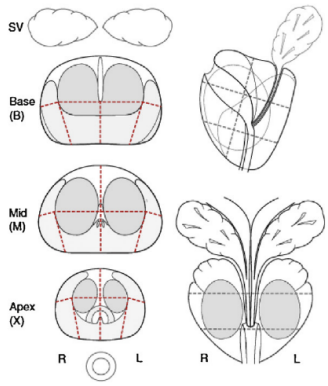
4.3.1.3 The PRECISE case report form

Finally, a dedicated PRECISE case report form (shown in Fig. 15) was developed to facilitate the collection of clinical and imaging data needed to inform cohort analysis in a proper manner.

PRECISE Case report form for men having MRI on active surveillance

Reporting radiologist		Date of scan		Date of report	
PSA		PSA date		PSA density	
Prostate volume on T2-weighted imaging		Magnet strength		Coil used	
Likelihood of clinically significant disease (1-5)*		PI-RADS 2 score (maximal)		TNM stage	
Likelihood of extraprostatic extension (T3a) (1-5)*		Likelihood of seminal vesicle invasion (T3b) (1-5)*			



Draw and number each lesion on the diagram, with the most significant lesion being number 1.

Lesion	Appeared since last scan?	Not visible	D1	D2	D3	Volume (D1 x D2 x D3 x 0.52)	Volume by planimetry	Likelihood of clinically significant disease (1-5)*	PI-RADS-2 score
1									
2									
3									

	Sequence where lesion best seen	Volume where lesion best seen	Volume on T2-weighted imaging
Lesion 1			
Lesion 2			
Lesion 3			

*Likert score of 1-5 for likelihood where 1= Very low likelihood; 2= Low likelihood 3 = Intermediate/equivocal; 4 = High likelihood ; 5 = Very high likelihood

	Date of previous MRI	Likelihood of change from previous MRI (1-5 score)	Parameter which has changed eg volume on T2W-I, visibility on DWI, Likert score or PI-RADS score, T3a or T3b disease
Lesion 1			
Lesion2			
Lesion 3			

Fig. 15 *- Case report form for reporting of magnetic resonance imaging at baseline and during follow-up in men on active surveillance. MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; PSA = prostate-specific antigen; T2W-I = T2-weighted image. Reprinted with permission from [4].*

4.3.2 Creating a dedicated software for serial mpMRI reporting

All lesions were visible, apart from one in the Dutasteride arm that was not detectable on DWI.

4.3.2.1 Comparison between MIM ® and Osirix ® in the MAPPED population

Median tumour volumes, ADC values and conspicuity from the two software programmes at both time points are shown in Table 21 (next page).
No significant differences between the two methods were observed for all parameters. However, there was a significant reduction in the reporting time at 6 months using the PRECISE reporting tool (12′33″ vs 10′52″, respectively; p = 0.005).

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Table 21 *- Median tumour volumes, ADC values, conspicuity and reporting time calculated using Osirix® and MIM® for each time point for 20 patients.*

	Baseline			6 months		
	Osirix ®	MIM ®	p	Osirix ®	MIM ®	p
T2-WI volume (cc)	0.29 (0.17-0.57)	0.32 (0.14-0.66)	0.72	0.23 (0.15-0.51)	0.30 (0.18-0.54)	0.28
DWI volume (cc) *	0.23 (0.14-0.35)	0.27 (0.16-0.45)	0.28	0.27 (0.12-0.48)	0.30 (0.11-0.49)	0.29
DCE volume (cc)	0.31 (0.26-0.60)	0.39 (0.24-0.68)	0.28	0.27 (0.10-0.64)	0.34 (0.12-0.60)	0.96
ADC lesion * (x 10^{-3} mm^2/s)	0.90 (0.86-1.04)	0.84 (0.76-1.06)	0.29	1.01 (0.87-1.07)	0.93 (0.81-1.18)	0.49
ADC PZ * (x 10^{-3} mm^2/s)	1.53 (1.41-1.64)	1.56 (1.48-1.70)	0.78	1.49 (1.39-1.61)	1.49 (1.42-1.62)	0.72
Conspicuity §	1.59 (1.37-1.83)	1.73 (1.4-2)	0.28	1.49 (1.33-1.83)	1.60 (1.27-2.10)	0.29
Reporting time (mins and sec)	14’47’’ [10’20’’ - 17’37’’]	14’34’’ [11’45’’- 16’42’’]	0.66	12’33’’ [09’14’’ - 16’18’’]	10’52’’ [08’41’’-13’56’’]	0.005

Note – Data are medians and 1st and 3rd interquartile ranges (parentheses); T2-WI: T2-weighted imaging; DWI: diffusion-weighted imaging; DCE: dynamic contrast enhanced; ADC: apparent diffusion coefficient; PZ: peripheral zone.

** Data from 19 patients.*

§ Conspicuity was defined as the mean ADC of the peripheral zone divided by the mean ADC of the tumour on DWI.

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Similar results were found analysing the placebo (n=10) and the dutasteride (n=10) arms independently (Table 22 and Table 23, respectively, next two pages), with a significant difference in the reporting time for the Dutasteride arm using the PRECISE reporting tool (15′50″ vs 12′59″; p = 0.01).

Table 22 *- Median tumour volumes, ADC values, conspicuity and reporting time calculated using Osirix® and MIM® for each time point in the placebo arm (n=10).*

	Baseline			6 months		
	Osirix ®	MIM ®	p	Osirix ®	MIM ®	p
T2-WI volume (cc)	0.29 (0.13-0.44)	0.27 (0.15-0.44)	0.58	0.24 (0.17-0.41)	0.30 (0.22-0.44)	0.28
DWI volume (cc)	0.19 (0.15-0.27)	0.20 (0.16-0.33)	0.36	0.26 (0.12-0.33)	0.27 (0.14-0.35)	0.58
DCE volume (cc)	0.30 (0.27-0.52)	0.34 (0.24-0.58)	0.36	0.19 (0.10-0.46)	0.34 (0.09-0.45)	0.88
ADC lesion ($\times 10^{-3}$ mm^2/s)	0.89 (0.86-1.04)	0.91 (0.72-1.16)	0.81	0.94 (0.87-1.07)	0.98 (0.78-1.06)	0.68
ADC PZ ($\times 10^{-3}$ mm^2/s)	1.58 (1.34-1.63)	1.59 (1.55-1.71)	0.46	1.50 (1.41-1.61)	1.50 (1.44-1.68)	0.66
Conspicuity §	1.59 (1.33-1.77)	1.65 (1.43-1.82)	0.56	1.55 (1.45-1.97)	1.61 (1.38-1.98)	0.69
Reporting time (mins and sec)	11’59’’ [10’06’’ - 15’09’’]	12’53’’ [10’55’’- 15’24’’]	0.36	10’47’’ [08’46’’ - 12’38’’]	9’28’’ [08’30’’ - 11’59’’]	0.36

Note – Data are medians and 1st and 3rd interquartile ranges (parentheses); T2-WI: T2-weighted imaging; DWI: diffusion-weighted imaging; DCE: dynamic contrast enhanced; ADC: apparent diffusion coefficient; PZ: peripheral zone.

§ Conspicuity was defined as the mean ADC of the peripheral zone divided by the mean ADC of the tumour on DWI.

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Table 23 *- Median tumour volumes, ADC values, conspicuity and reporting time calculated using Osirix® and MIM® for each time point in the Dutasteride arm (n=10).*

	Baseline			6 months		
	Osirix ®	MIM ®	p	Osirix ®	MIM ®	p
T2-WI volume (cc)	0.43 (0.25-0.7)	0.48 (0.19-0.68)	0.93	0.33 (0.16-0.57)	0.31 (0.17-0.54)	0.93
DWI volume (cc) *	0.27 (0.14-0.52)	0.44 (0.21-0.5)	0.24	0.47 (0.08-0.49)	0.37 (0.11-0.59)	0.58
DCE volume (cc)	0.46 (0.26-0.75)	0.53 (0.28-0.79)	0.40	0.42 (0.16-0.64)	0.42 (0.18-0.59)	0.93
ADC lesion * (x 10^{-3} mm^2/s)	0.91 (0.86-1.04)	0.84 (0.78-0.88)	0.24	1.01 (1-1.06)	0.92 (0.84-1.18)	0.39
ADC PZ * (x 10^{-3} mm^2/s)	1.51 (1.43-1.65)	1.50 (1.48-1.56)	0.71	1.49 (1.41-1.58)	1.46 (1.39-1.51)	0.93
Conspicuity §	1.59 (1.46-1.83)	1.77 (1.54-2)	0.24	1.41 (1.32-1.52)	1.50 (1.27-1.70)	0.39
Reporting time (mins and sec)	17’52’’ [13’25’’ – 19’59’’]	16’35’’ [13’28’’- 19’48’’]	0.57	15’50’’ [11’44’’ - 19’02’’]	12’59’’ [09’28’’ – 16’03’’]	**0.01**

Note – Data are medians and 1st and 3rd interquartile ranges (parentheses); T2-WI: T2-weighted imaging; DWI: diffusion-weighted imaging; DCE: dynamic contrast enhanced; ADC: apparent diffusion coefficient; PZ: peripheral zone.

** Data from 9 patients.*

§ Conspicuity was defined as the mean ADC of the peripheral zone divided by the mean ADC of the tumour on DWI.

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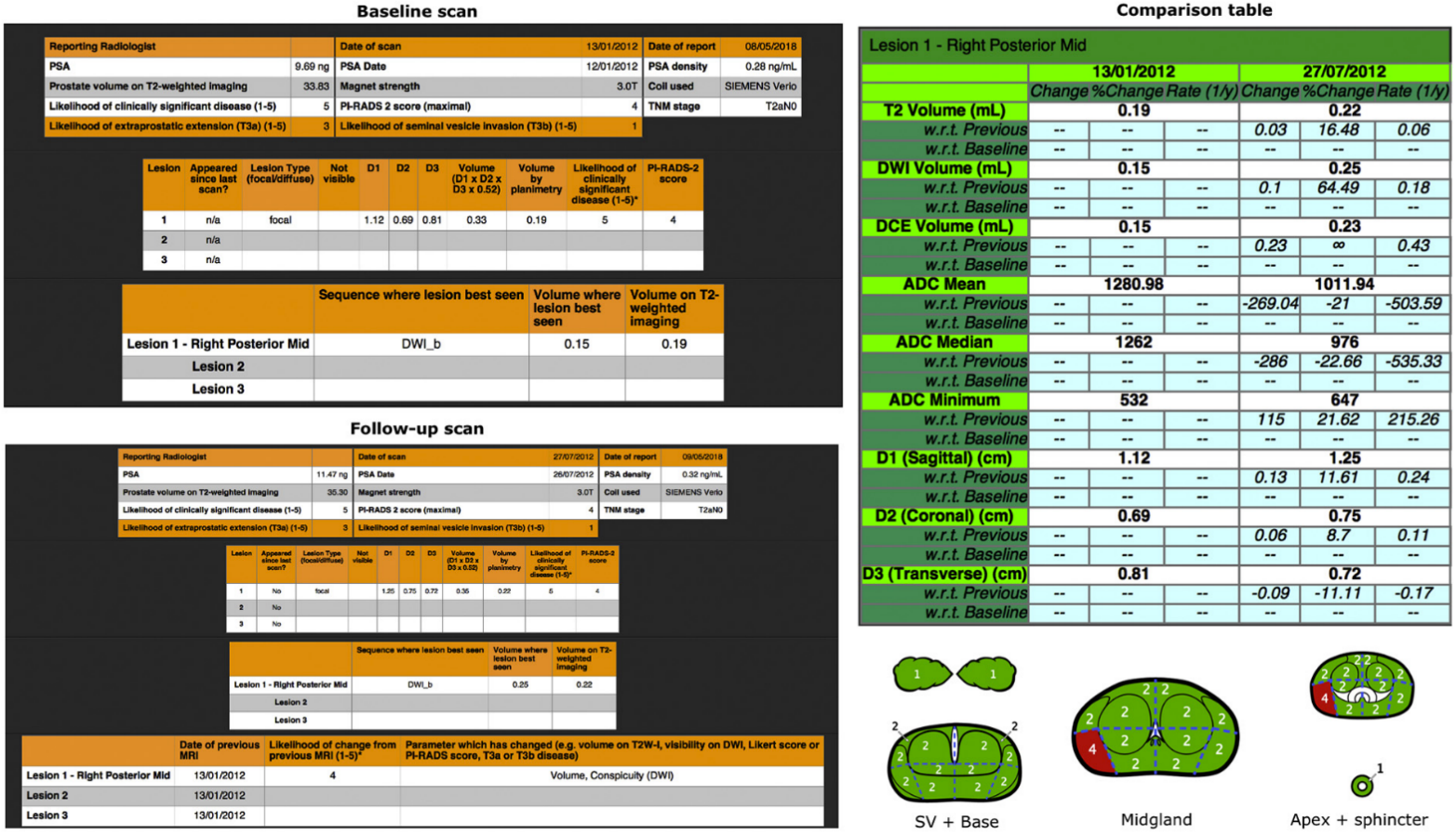
4.3.2.2 The PRECISE structured report

A structured report with baseline and follow-up data was also created using the PRECISE reporting tool (Fig. 17, next page), in line with the PRECISE case report form previously shown in Fig. 16.

Figure 16 *- Structured reports using a dedicated reporting tool according to the PRECISE recommendations of the same patient shown in Fig. 2. The images show data from baseline and follow-up scans together with a comparison table (including the rate of increase/decrease) of the key parameters of the lesion from each scan and a diagram showing lesion location and PI-RADS v.2 score (in red).*



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4.4 Discussion

This chapter presents the results of the PRECISE consensus meeting including the recommendations, and the application of a dedicated PRECISE reporting software to allow automated comparison between sequential mpMRI scans on AS in the MAPPED population.

We have seen that identifying men who have been diagnosed with low- or intermediate-risk prostate cancer but have disease that is progressing rapidly, or men who have the highest risk of progressing to higher-risk clinically significant prostate cancer that requires treatment, is extremely important in the management of patients on AS.

The key points from the PRECISE consensus meeting were: i) to identify a list of key items in the PRECISE checklist describing what should be reported in studies of serial mpMRI during AS in order to improve the reporting standards of these studies; ii) to create a scoring system (PRECISE score) able to assess radiological change over time; iii) to recommend a diagrammatic report and have a standard dataset for the serial reporting of mpMRI in men on AS.

First of all, investigators should use the PRECISE checklist when designing and discussing their results from the application of mpMRI during AS. The PRECISE checklist provides a guide for authors in preparing a manuscript for publication and for reviewers and editors when assessing manuscripts and should be always used for reporting a cohort of men receiving serial mpMRI during AS.

If we have a closer look at the PRECISE checklist (Table 19), the identification of the study as one of reporting results from mpMRI in men on AS (either to identify men as suitable for AS or as a tool for repeat assessment on AS) in the title is important.

The setting, location, and recruitment period and study design should be also reported and the inclusion and exclusion criteria with the maximum Gleason score, maximum PSA, and the name, version, and citation of an established AS protocol should be stated.

In addition to this, the requirement for confirmatory biopsy, frequency of PSA testing, and the indication and frequency for biopsy and mpMRI should be always mentioned. This is of utmost importance, as we have seen in Chapter 2 that there is still huge variability across the world in terms of AS inclusion criteria, and frequency of biopsy and mpMRI. [9]

From a radiological point of view, the panellists agreed that the studies dealing with mpMRI and AS should clearly state if they meet (or do not meet) the minimum criteria set by national/international guidelines. It follows that detailed information regarding technical parameters (e.g., field strength, coils, in-plane resolution, slice thickness, highest *b*-value acquired for DWI and temporal resolution for DCE images) should be always included.

Of note, there was much debate about what constitutes radiological progression. The panellists were not able to agree on one single definition and it should be noted that the 1-to-5 scale (i.e., the PRECISE score) that was created to assess radiological

progression is not stringent at this regard.

For example, it was acknowledged that tumour size can be measured using different definitions:

i) by volume (by planimetry)
ii) by volume (calculated using the ellipsoid formula from three diameters)
iii) by biaxial measurement of maximum diameters on an axial slice
iv) by a single measurement of maximum diameter

At that time, the panellists felt that there was insufficient evidence to determine the optimal measurement for distinguishing between measurement errors or true disease progression, as some believed that planimetry volume would be most accurate but other panellists acknowledged that this would be too time consuming. It should be noted that when the panellists met in February 2016 there were no robust data on how to assess a significant change in tumour size or conspicuity during AS, and they all agreed that comparative data from the same cohort on the reproducibility of different size measurements (e.g., planimetry volume and biaxial diameter) or conspicuity using the PRECISE case report would allow such data to be acquired.

As far as the histology is concerned, it was agreed that Gleason score and maximum cancer core length were important determinants of clinically significant prostate cancer during AS, but there was no agreement on a specific cut-off. However, it was agreed that Gleason ≥ 4+ 3, ≥ T3a disease or any nodal involvement/bone

metastases should be all considered clinically significant prostate cancer.

As expected, there were some significant areas of uncertainties that should be mentioned. The first is that there was no agreement on the best way to present change in lesion size or appearance over time, as it was acknowledged that some lesions (especially very small lesions) could become non-visible during follow-up, and there was uncertainty over how best to address this when combining results all together. Moreover, one should acknowledge that some centres exclude men with visible lesions on mpMRI from AS to reduce the likelihood of unfavourable pathology. [10,11]

The panellists did not agree on whether repeat standard biopsy and/or targeted biopsy should be performed on men with no radiological changes over time; some experts felt that a man eligible for treatment at AS entry (e.g. small-volume Gleason 3 + 4) would not require additional biopsies in the absence of radiologic change, as there are data suggesting that radiological stability can predict Gleason score stability. [12]

It was also recognised that in the presence of suspected radiological progression patients and clinicians could opt for treatment without further biopsy.

A prerequisite to carry out serial mpMRI reporting of our AS cohort was the conceptualisation and development of a dedicated PRECISE reporting software for use in men on AS. As previously stated, this has been possible thanks to my close collaboration with MIM® company during the last three years.

Thanks to my knowledge on the topic, I gave them my input to develop a dedicated software that maximises the radiologist's expertise in identifying the ROIs that are suspicious on mpMRI and reduces the time to produce a PRECISE compliant report by using contouring aids (e.g., marking the centre of a previously identified lesion on a subsequent MRI scan and calculating change in size over time).

More in detail, we have seen that, when compared to a widespread commercially available platform (Osirix®), the reporting time of the follow-up scan in the MAPPED trial was quicker using the semi-automated PRECISE reporting workflow both in the whole population and in the arm exposed to antiandrogen therapy.
The main explanation lies in the ability of this tool to transfer the contours from one scan to the other and to show the previous lesion location, with a significant drop in the time needed for contouring the follow-up scan.

We have also seen that the MIM Software is able to produce a specific report at baseline and at each additional time point that includes clinical and imaging data according to the PRECISE case report, as well as a comparison table between lesion characteristics at baseline and follow-up scans.

Two main consequences derive from the use of a dedicated PRECISE reporting tool. The first is that specific tools like this can contribute to the creation of a cloud-based platform for multiple centres with multiple readers in order to analyse data from different cohorts on AS, as advocated by the panellist who drafted the PRECISE recommendations [4], and this will be extremely useful to validate PRECISE at an international level.

The second is that the use of the PRECISE tool allows reporting of serial MRI scans on AS more efficiently and all the ROIs generated by the radiologists could be used in the future to inform machine learning across different AS cohorts.
In addition to this, the comparison tables that derive from a dedicated PRECISE reporting tool could help in the identification of specific thresholds to define radiological changes on mpMRI in a multi-centre and large-scale dataset, allowing patients at lowest risk to receive less frequent testing but at the same time guaranteeing that any radiological signs of higher risk disease can be identified in a timely manner prompting biopsy and/or treatment.

4.4.1 Limitations

The PRECISE recommendations mirror the opinions of only a small group of panellists, despite all of them were highly experienced clinicians who were internationally renowned for their work in prostate cancer (and AS in particular). Although the scoring was anonymous, the face-to-face discussion was not, and some panellists could have influenced the debate. However, both the fact of having an independent chair and of scoring the items anonymously did reduce the chances of this being a limitation.

It should be also acknowledged that the PRECISE reporting tool that has been created for serial mpMRI reporting has been compared to only one other platform (Osirix®), but we know that many other platforms are available on the market. However, at present, the PRECISE reporting tool is the only dedicated software

programme for serial reporting of mpMRI on AS according to the PRECISE recommendations and it will be interesting to compare our results with those from other dedicated dedicated reporting platforms once these will be available.

4.4.2 Conclusions

In conclusion, the PRECISE recommendations and case report form should be used to report serial mpMRI scans in men on AS so as to assess radiological change over time.

In order to understand the full potential of mpMRI during AS, the panellists highlighted the need of a robust data analysis across different cohorts to determine the clinical significance of radiological change over time.

To do this, there is a need of novel reporting software programmes to assist the radiologist in the reporting of sequential mpMRI scans according to the PRECISE recommendations and in the automated comparisons across a patient over time.

The MIM® PRECISE reporting tool that we have created with an industrial partner is the first software of this kind and demonstrates how dedicated software programmes can be of huge help to analyse large data sets, allowing a quicker assessment and refinement of the PRECISE recommendations.

At present, the seminal paper on the PRECISE score [4] has been cited 134 times (Google Scholar).

4.5 Related publications

1. Moore CM *, Giganti F *, Albertsen P, et al. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations - A Report of a European School of Oncology Task Force. Eur Urol (2017); 71:648-655. * *shared first authorship*

2. Giganti F, Allen C, Piper JW, et al. Sequential prostate MRI reporting in men on active surveillance: initial experience of a dedicated PRECISE software program. Magn Reson Imaging (2018); 57:34-39.

3. Giganti F, Kirkham A, Allen C, et al. Update on multiparametric prostate MRI during active surveillance: current and future trends and role of the PRECISE recommendations. AJR July 29, 2020. Accepted manuscript (in press) doi:10.2214/AJR.20.23985

4.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study design (publication 1, 2 and 3): in particular, I applied the UCLA/RAND methodology in publication 1.

- Acquisition of data: (publication n. 1, 2 and 3): in particular, I created the summary graphs for each item for both rounds and transcribed all the responses to a database for analysis.

- Statistical analysis: (publication n. 1 and 2)

- Interpretation of data and writing (publication n. 1, 2 and 3): in particular, I was responsible for the analysis and interpretation of the data together with my supervisor, Professor Caroline M Moore, with whom I share first authorship in publication n. 1.

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1, 2 and 3): in particular, Professor Moore contributed to the study design, data interpretation and obtained funding for publication n. 1.
- All the panellists who participated to the PRECISE consensus meeting, as reported in Table 17 (publication n. 1)
- Mr Jonathan Piper and Mr David Mirando from MIM® (publication n. 2)
- Dr Alex Kirkham (publication n. 3)
- Dr Clare Allen (publication n. 3)

4.7 References

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[8] Giganti F, Kirkham A, Allen C, et al. Update on multiparametric prostate MRI

during

active surveillance: current and future trends and role of the PRECISE recommendations. AJR July 29, 2020. Accepted manuscript (in press) doi:10.2214/AJR.20.23985

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Chapter 5 Application of the PRECISE recommendations in the UCLH cohort

In this chapter I present the results of the application of the PRECISE scoring system in the whole cohort of patients with prostate cancer on AS at our Institution.

Some preliminary findings have been published in *Prostate Cancer and Prostatic Disease* [11]. The findings related to the PRECISE recommendations have been published in *European Radiology* [3] and in the *British Journal of Radiology* [6].

5.1 Introduction

In Chapter 4 we have seen that the key features of the PRECISE recommendations are the measurement of each lesion at every time point, and the assessment of the likelihood of radiological progression using a 1-to-5 scale (PRECISE score).

This chapter is focussed on the application of the PRECISE recommendations in our cohort at UCLH, which is one of the largest MR-based AS cohorts in the world. I will also discuss the relationship between the different types of lesion measurement on mpMRI and the PRECISE score, as advocated by the PRECISE working group in 2016.

We know that the two most relevant questions during AS are:

- What constitutes a radiologically significant lesion during AS?
- What is a significant (clinically meaningful) change on MRI?

Over the last two years, there have been five different groups (including the results from my PhD at UCL) that have reported the PRECISE criteria in their AS cohorts [1-5], and their key findings are reported in Table 24.

Table 24 *– Current studies that have published PRECISE reports*

Authors	Year	Country	Cohort (n)	Time period	AS inclusion criteria (Gleason)	Median Follow up (months)	Mp-MRI	Likert or PI-RADS	Follow-up biopsy	Definition of progression	Sensitivity Specificity Positive predictive value Negative predictive value	Key message
Dieffenbacher et al. [1]	2019	Germany	158	2010-2018	Only 3 + 3	48	Yes	PI-RADS	Yes	GS ≥ 3 + 4, PSA ≥ 10 ng/ml, three or more positive biopsy cores, PSA density > 0.2 ng/ml, or clinical stage ≥ T2b.	NA	No patients with PRECISE 1-2 (n=57) are disqualified from AS. Re-biopsy only PRECISE ≥ 3.
Caglic et al. [2]	2020	UK	295	2011-2018	≤ 3+4	52	Only at baseline, then bp-MRI.	Likert	Yes	One-step upgrade between diagnostic and repeat biopsy for low and	76 % 89 % 52 % 96 %	PRECISE scores ≤ 1-3 have high negative predictive value, which may reduce

										intermediate prostate cancer and MRI stage progression		the need for re-biopsy.
Giganti et al. [3]	2020	UK	553	2005-2020	≤ 3+4	76	Yes	Both PI-RADS and Likert	Not for all	Histological progression to ≥ Gleason score 4 + 3 (Gleason Grade Group 3) and/or initiation of active treatment.	87 % 77 % 65 % 92 %	PRECISE 1-3 during AS have a very low likelihood of clinical progression and many can avoid routine re-biopsy. PRECISE 4-5 show a trend to an increase in PSA density.
O'Connor et al. [4]	2020	USA	391	2007-2020	≤ 3+4	35.6	Yes	In-house score and PI-RADS (after 2015)	Yes	GG1 to ≥ GG2 GG1 to ≥ GG3 GG2 to ≥ GG3	53 % 64 % 38 % 76 % 65 % 62 % 15 % 94 % 67 % 59 % 32 % 86 %	PRECISE 1-3 have a low probability of detecting progression from GG1 to ≥ GG3 on biopsy. Elevated PSA density increases the risk of cancer progression despite stable MRI.

Ullrich et al. [5]	2020	Germany	55	2011-2017	≤ 3+4	19	Yes	PI-RADS	Yes	One-step upgrade between diagnostic and repeat biopsy for low and intermediate prostate cancer.	100 % 42 % 66 % 100 %	No PRECISE 1-3 are upgraded at follow-up biopsy.

Legend – AS: active surveillance; Mp-MRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; bp-MRI: biparametric magnetic resonance imaging; PSA: prostate specific antigen; GGG: Gleason grade Group. Reprinted with permission from Giganti F, Kasivisvanathan V, Allen C and Moore CMM. The Importance of Being PRECISE in Prostate Magnetic Resonance Imaging and Active Surveillance. Eur Urol (2021) (in press). doi: 10.1016/j.eururo.2021.01.016

We note that there are some differences between these cohorts, from inclusion criteria to follow up schedule, the most important being the exclusion of Gleason 3+4 disease [1], the routine use of confirmatory biopsy [3], the absence of contrast at follow up imaging [2] and the use of the PI-RADS score, with two centres using only a Likert scoring system [2, 4] (although the use of a Likert scale is allowed by the PRECISE criteria).

Despite the differences in AS protocols and MR reporting, all studies [1-5] draw the same conclusion, which is that patients with stable MRI (i.e., PRECISE 1-3) and stable PSA kinetics should avoid routine re-biopsy. Due to the different definitions of progression (Table 24), ranging from a PSA > 10 ng/ml at the lowest risk range to biopsy finding of Gleason 4+3, or initiation of active treatment, the positive predictive values range from 52 % to 66 %, meaning that rebiopsy is often helpful. Some centres will not insist on repeat biopsy prior to active treatment, for example where a man has Gleason 3+4 at baseline and a PRECISE score of 4 or 5.

In our cohort, clinical progression has been defined as a combined endpoint of either histological progression to GGG 3, or initiation of active treatment, in line with our clinical practice at UCLH.

Differently from the other three studies that have applied the PRECISE recommendations so far [1,2,4,5], in our MRI-led AS programme, biopsies are not offered on a protocol basis but ‘for cause’, as the triggers for the recommendation include adverse changes in mpMRI or PSA kinetics. Although our protocol differs from the other published protocols, we know that compliance rates with protocol biopsy can be as low as 30% both in clinical practice and in studies such as PRIAS

[6], and actually the biopsy rates of the two approaches are more similar than the protocols would suggest [7,8].

I will now present and discuss in more detail:

i) the results from the systematic application of the PRECISE criteria and case report in our AS cohort at UCLH using the dedicated MIM® reporting tool that has been discussed in the previous chapter.

ii) the results from the comparison of the different measurements for prostate cancer during AS using tumour volume by planimetry as the reference standard, as advocated by the panellists of the PRECISE working group.

5.2 Materials and Methods

5.2.1 Patient population

As discussed in Chapter 2, at UCLH we have a clinical image guided AS cohort that was established in 2005 in a prospective manner, as our Institution was one of the first units to use MRI in prostate cancer diagnosis.

Currently, this cohort is one of the largest of its kind in the world and includes more than 630 patients who have had a prostate mpMRI and biopsy-confirmed low to intermediate-risk prostate cancer (i.e., ≤ Gleason 3+4 and PSA ≤ 20 ng/ml) as per UK NICE guidelines, and who have chosen AS as their initial management option, as shown in Fig. 7 in Chapter 2.

All clinical records and MR images are routinely reviewed as part of an audit performed for the internal evaluation of the AS service, including the image quality of MR scans.

5.2.2 Primary outcome

My hypothesis for the primary outcome was the following:

- **P**atient: In patients with low or intermediate-risk prostate cancer on AS
- **I**ntervention: does the PRECISE score
- **C**omparator: compared with histological progression to ≥ GGG 3 and/or initiation of active treatment

- **O**utcome: predict clinical progression (defined by histological progression to ≥ GGG3 and/or initiation of active treatment)?

5.2.3 Secondary outcome

My hypothesis for the secondary outcome was the following:

- **P**atient: In patients with low or intermediate-risk prostate cancer on AS
- **I**ntervention: which one among different tumour measurements (i.e., single diameter, biaxial measurement and ellipsoid formula)
- **C**omparator: compared with planimetry on MRI
- **O**utcome: is best associated with radiological progression (PRECISE score)?

The subcohort included in this analysis was the result of more stringent criteria than the ones for the primary outcome, such as: i) only men with a visible lesion scoring PI-RADS ≥ 3; ii) only two mpMRI scans (baseline and follow-up, with the latter being the most recent if multiple scans had been performed over the years) and iii) diagnosis of prostate confirmed *exclusively* by targeted biopsy.

5.2.4 MR protocol

Three different scanners were used: two 1.5T (Symphony or Avanto, Siemens) and one 3T (Achieva, Philips) MR system, with a pelvic phased-array coil. The multiparametric protocol comprised T2-WI, DWI and DCE imaging, as shown in Table 25.

Table 25 *- MR imaging parameters at our Institution*

	1.5T	3T
T2-weighted imaging (axial)		
Sequence	TSE	TSE
Field of view (mm)	200	180
Slice thickness (mm)	3	3
Matrix size	256 x 256	300 x 300
Pixel size (mm x mm)	0.8 x 0.8	0.6 x 0.6
TE (ms)	95	100
TR (ms)	5340	5407
Acquisition time	4min 2sec	5min 13sec
Diffusion-weighted imaging		
Sequence	SSEPI	SSEPI
Field of view (mm)	320	220
Slice thickness (mm)	5	5
Matrix (read)	172 x 172	168 x 168
Pixel size (mm x mm)	1.5 x 1.5	1.29 x 1.29
TE (ms)	101	80
TR (ms)	2200	2304
Multiple *b*-values (s/mm^2)	0, 150, 500, 1000	0, 150, 500, 1000
Acquisition time	5min 44sec	6min 15sec
High *b*-values (s/mm^2)	1400	2000
Acquisition time	3min 39sec	2min6sec
Dynamic contrast enhanced		
Sequence	3D FLASH	T1-FFE
Field of view (mm)	260	180
Matrix (read)	192 x 192	140 x 162
Pixel size (mm x mm)	1.4 x 1.4	1.29 x 1.30
TE (ms)	2.50	2.8
TR (ms)	5.61	5.8
Fat suppression	Fat sat	SPAIR
Acquisition time	5min 43sec	3min11sec
Temporal resolution (sec)	13	13

Legend: TSE: Turbo Spin Echo; TE: echo time; TR: repetition time; SSEPI: single shot echo planar imaging; FLASH: Fast low angle shot; FFE: fast field echo; SPAIR: Spectral attenuated inversion recovery.

5.2.5 MR analysis and PRECISE score assessment

I have been retrospectively re-reporting all scans of our AS cohort according to the PI-RADS v.2 guidelines [9] and the PRECISE recommendations over the last three years. I was privy only to PSA and initial biopsy results but blinded to the original MRI reports.

As previously mentioned, I used the dedicated reporting tool (MIM® Symphony Dx v. 6.8.3) that I co-developed with MIM®, as shown in Chapter 4. At the second and subsequent scans, I also assessed the PRECISE score for the likelihood of radiological progression from the last scan using different MR features (conspicuity, increase in volume, signs of extracapsular extension or seminal vesicle invasion).

I reported all lesions for each scan but in the case of multifocal disease, the lesion with the highest PI-RADS score was the index lesion included in the analysis, and where there was more than one lesion at that score, the lesion with the highest volume was deemed the index lesion.

In addition to this, as there are still no explicit recommendations on which PRECISE score should be considered the most representative when multiple scans are acquired, I used the highest PRECISE score for each patient during the study period in this analysis.

I applied the PRECISE recommendations as below:

- PRECISE 3: scans with a visible lesion showing stable mpMRI features over time, or a persistent negative scan
- PRECISE 4: a new lesion in a previous negative scan or if a lesion was not visible at baseline imaging but appeared on a subsequent scan and then had stable MR features over time (i.e., in this case the highest PRECISE score was the most representative)

As acknowledged in the PRECISE recommendations, the index lesion during AS can be measured using different techniques:

i) by planimetry (i.e., contouring the lesion slice by slice)
ii) using the ellipsoid formula [i.e. (anteroposterior X transverse X longitudinal diameter) * π/6]
iii) by biaxial measurement of maximum diameters (i.e., estimated square area)
iv) by single maximum diameter.

As there are still no specific recommendations on the most accurate measurement of tumour size during AS, I compared data from T2-WI according to all four different definitions.

5.2.6 Statistical analysis

I report continuous variables summarised by medians and interquartile ranges and categorical variables by frequencies and percentages.

For the primary outcome, I used the Mann-Whitney test and Wilcoxon test to determine the statistical significance of differences. Because the PRECISE score could change over time with each successive scan at different time points, I included a time-dependent covariate for the PRECISE score using a Cox model predicting disease progression, where time zero was the date of the first biopsy showing prostate cancer. I assessed progression-free survival using Kaplan-Meier curves and I used log-rank test to assess differences between curves. I tested the interaction term between each follow-up MRI and the corresponding PRECISE score, both considered time-dependent covariates, to explore the variation of PSA density over time according to PRECISE score using linear regression and locally weighted scatterplot smoothing.

To assess the secondary outcome, I used Spearman's rank correlation coefficients between tumour volume by planimetry (reference standard) and the other three measurements. I used Bland–Altman plots to measure the agreement between tumour volume by planimetry and the ellipsoid formula.

Given the different time frames between the two mpMRI scans for each patient, I adjusted tumour growth rate for the intervening time interval in years (i.e. [baseline volume – follow- up volume/baseline volume] * 100, per year) and I plotted the relative percentage change on a waterfall plot according to the PRECISE score. I compared this change was compared between the different groups using the Wilcoxon rank sum and Kruskal–Wallis tests.

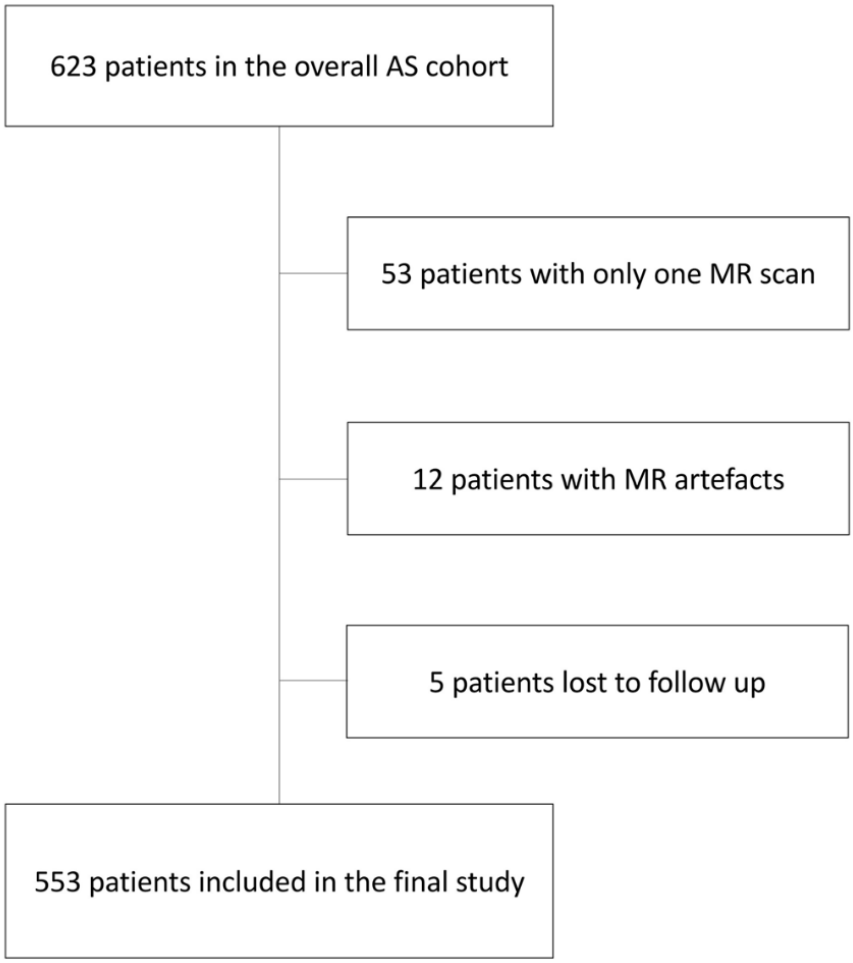
I performed statistical analyses using R software (Version 3.4.2; Foundation for Statistical Computing). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

5.3 Results

5.3.1 Primary Outcome – relationship between the PRECISE score and clinical progression

The total cohort comprised 553 patients on AS who received two or more serial mpMRI scans between December 2005 and January 2020, as shown in Fig. 17.

Fig. 17 *- Flowchart shows study enrolment. Legend - AS: active surveillance; MR: magnetic resonance. Reprinted with permission from [4]*



The total number of mpMRI scans that I have re-reported is 2,161.

In total, 232/553 (42%) patients were exclusively scanned on a 1.5T and 8/553 (1.4%) exclusively on a 3T scanner.

Table 26 shows the number of men and scans included in the study.

Table 26 *- number of patients and MR scans included in the study*

Number of MR scans	Number of patients (n = 553)
2	112 [20%]
3	141 [25%]
4	121 [22%]
5	104 [19%]
6	42 [8%]
7	18 [3%]
8	7 [1.4%]
9	5 [1%]
10	1 [0.2%]
11	1 [0.2%]
12	1 [0.2%]

Legend: Percentages in brackets [%].
The median number of scans per patient was 4 [IQR: 3-5].
The median interval time between baseline and the second scan was 14 months [IQR: 11-22].
Reprinted with permission from [3]

The median follow-up of the overall population was 76 months (52 - 100.5). Overall, 165/553 (30%) patients experienced the primary outcome of clinical progression. The median follow-up of those without clinical progression was 74.5 months (53 - 98).

Table 27 (next page) shows baseline and follow-up characteristics of the population. Overall, 306/553 (55%) patients had at least one additional biopsy, 178 (58%) of which were targeted by visual registration. For patients with baseline PI-RADS 4 and 5 lesions (n = 183), 133/183 (73%) had Gleason 3 + 3 and 50/183 (27%) had Gleason 3 + 4 at entry biopsy. Of them, 49/183 (27%) had a targeted biopsy at entry.

Table 27 *- Descriptive statistics of all patients included in the study and stratified by no additional biopsy and biopsy progression, which is defined as one step in Gleason score upgrade (including those men with Gleason 3+3 at entry and subsequent Gleason 3+4). P values refer to 'no biopsy progression' vs 'biopsy progression'.*

	Overall (n=553)	**No additional biopsy (n=247)**	**No biopsy progression (n=177)**	**Biopsy progression (n=129)**	*p*
Age at diagnosis (years)	62 (56 - 67)	62 (56 - 67)	62 (57 - 66)	62 (56 - 67)	0.60
PSA at baseline MR (ng/ml)	6.3 (4.7 - 8.4)	6.3 (4.53 - 8.80)	6.51 (4.88 - 8.30)	6 (4.7 - 8.6)	0.47
Prostate volume at baseline MR (cc)	45.8 (32.7- 63.4)	48.15 (33.47 - 67.11)	47.93 (36.15 - 64.38)	38.32 (29.3 - 56.7)	< 0.01
PSA density at baseline MR (ng/ml/ml)	0.12 (0.09 - 0.2)	0.11 (0.08 - 0.17)	0.12 (0.09 - 0.17)	0.15 (0.1 - 0.21)	0.01
Gleason score at entry					
3+3	445 [80]	188 [76]	136 [77]	119 [92]	0.02
3+4	108 [20]	59 [24]	41 [23] *	10 [7]	
Biopsy type at entry					
Transperineal template	89 [16]	62 [25]	18 [10]	9 [7]	
Transperineal + targeted	76 [14]	52 [21]	11[6]	13 [10]	NA
Systematic	330 [60]	109 [44]	128 [72]	93 [72]	
Systematic + targeted	35 [6]	15 [6]	12 [7]	8 [6]	
TURP	23 [4]	9 [4]	8 [5]	6 [5]	
Baseline PI-RADS score					
1-2	266 [48]	123 [50%]	98 [56]	45 [35]	
3	104 [19]	45 [18%]	36 [20]	23 [18]	< 0.01
4	164 [30]	74 [29%]	36 [20]	54 [42]	
5 **	19 [3]	5 [3%]	7 [4]	7 [5]	

Overall PRECISE score					
1	100 [18]	53 [21]	43 [24]	4 [3]	< 0.01
2	23 [4]	13 [5]	9 [5]	1 [1]	
3 (non-visible lesion)	152 [28]	97 [39]	50 [28]	5 [4]	
3 (visible lesion)	38 [7]	15 [7]	13 [7]	10 [8]	
4	211 [38]	61 [25]	56 [33]	94 [73]	
5	29 [5]	8 [3]	6 [3]	15 [11]	

Legend: Data are medians and interquartile range (parentheses); percentages in brackets [%]. PSA= Prostate Specific Antigen; NA= not applicable; MR = Magnetic Resonance; TURP: transurethral ultrasound resection of the prostate; PI-RADS: Prostate Imaging–Reporting and Data System; PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

** 18/41 [44%] discontinued AS: 16/18 showed radiological progression (fourteen PRECISE 4 and two PRECISE 5), fourteen of which showed also PSA progression. The remaining two patients showed PSA progression but no radiological progression.*

*** In the overall population, 13/19 patients had Gleason 3+3 and 6/19 had Gleason 3+4 at entry biopsy. In the 'no biopsy progression' group, 4/7 had Gleason 3+3 and 3/7 had Gleason 3+4 at entry biopsy. In the 'biopsy progression' group, all patients (7/7) had Gleason 3+3 at entry biopsy. In terms of lesion location, 4/19 were anterior lesions (two left anterior, one right anterior, one midline anterior) and the other 15/19 lesions were in the peripheral zone (8 on the left and 7 on the right).*

Reprinted with permission from [3]

Histopathological data stratified by PRECISE score are shown in Table 28 (next page).

Of 211 patients with PRECISE 4, 150 (71%) had repeat biopsy of which 94 (63%) were upgraded (Gleason ≥ 3+4), 22 with Gleason 3+4 at baseline had Gleason 3+4 on repeat biopsy, and 34/150 (23%) had Gleason 3+3 at baseline and were not upgraded.

Seventy out of 211 (33%) showed an increase in lesion size or conspicuity from baseline imaging, and 58/70 (83%) were upgraded on histology. Focusing on those patients with biopsy progression (Gleason ≥ 3+4) in the PRECISE 4 group (94/211; 45%), 36/94 (38%) developed a new lesion whilst 58/94 (62%) showed an increase in lesion size or conspicuity from baseline imaging. In this subcohort (n = 94), the median baseline PSA was 5.9 ng/ml (4.45 - 8.55) and the median baseline PSA density was 0.15 ng/ml/ ml (0.11 - 0.21).

***Table 28**: Histopathological data of the whole population according to PRECISE score*

		Number of biopsies			Gleason score at entry		Upgrade	
		Only diagnostic biopsy	At least one follow-up biopsy		3+3	3+4	Upgrade to GS 3+4	Upgrade to GS ≥ 4+3
PRECISE 1-2 (n=123)		66	57	Biopsy progression (n=5)	5	0	4	1
				No biopsy progression (n=52)	49	3	0	0
PRECISE 3 (n=190)	Stable visible lesion (n=38)	15	23	Biopsy progression (n=10)	9	1	8	2
				No biopsy progression (n=13)	9	4	0	0
	No visible lesion (n=152)	97	55	Biopsy progression (n=5)	4	1	4	0
				No biopsy progression (n=50)	43	7	0	0
PRECISE 4 (n=211)		61 **	150	Biopsy progression (n=94)	91*	3	80	14
				No biopsy progression (n=56)	34*	22	0	0
PRECISE 5 (n=29)		8 ***	21	Biopsy progression (n=15)	10	5	7	8
				No biopsy progression (n=6)	3	3	4	0

Legend

** Of the 125 patients who showed baseline Gleason 3+3 prostate cancer, 63/125 (50%) had a PI-RADS 4 lesion and 10/125 (8%) a PI-RADS 5 lesion at baseline MRI.*

*** 61 patients with a PRECISE score of 4 had no additional biopsy, and 26 progressed directly to active treatment. This was radical prostatectomy in 8, focal*

therapy in 8, radiotherapy in 5 and hormonal therapy in 3. The other two patients were put on watchful waiting.

**** 8 patients with a PRECISE score of 5 had no additional biopsy, and 5 progressed directly to active treatment. This was focal therapy in 2 and radiotherapy in 3. The other three patients had stage progression to T2a to radiological T3a and have chosen to continue with conservative management.*

Reprinted with permission from [3]

Table 29 reports the association between PI-RADS score at baseline and the PRECISE score at follow-up scans. We can see that PI-RADS 1 - 2 tended to be associated with PRECISE scores ≤ 3 whilst patients with higher PI-RADS baseline scores (i.e., PI-RADS 4 - 5) had more than a two-thirds chance of being attributed a PRECISE score 4 or 5, demonstrating that MRI visibility (PIRADS 4 - 5) shows a likelihood of progression of 68% (125/183) over a median of 76 months. Of the 370 men with no focal visible lesion 115 (31%) showed PRECISE progression scores of 4 - 5 over 76 months, giving a hazard (or odds ratio) for progression of 2.2 (about 2 i.e., 0.68/0.31)

	PI-RADS 1-2	PI-RADS 3	PI-RADS 4-5	Total
PRECISE 1-2	34	55	34	123
PRECISE 3	144	22	24	190
PRECISE 4-5	88	27	125	240
Total	266	104	183	553

Table 29 *- Relationship between baseline PI-RADS score and the highest PRECISE score from scans for each patient in the overall population (n = 553).*

Legend: PI-RADS: Prostate Imaging–Reporting and Data System; PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.Reprinted with permission from [3]

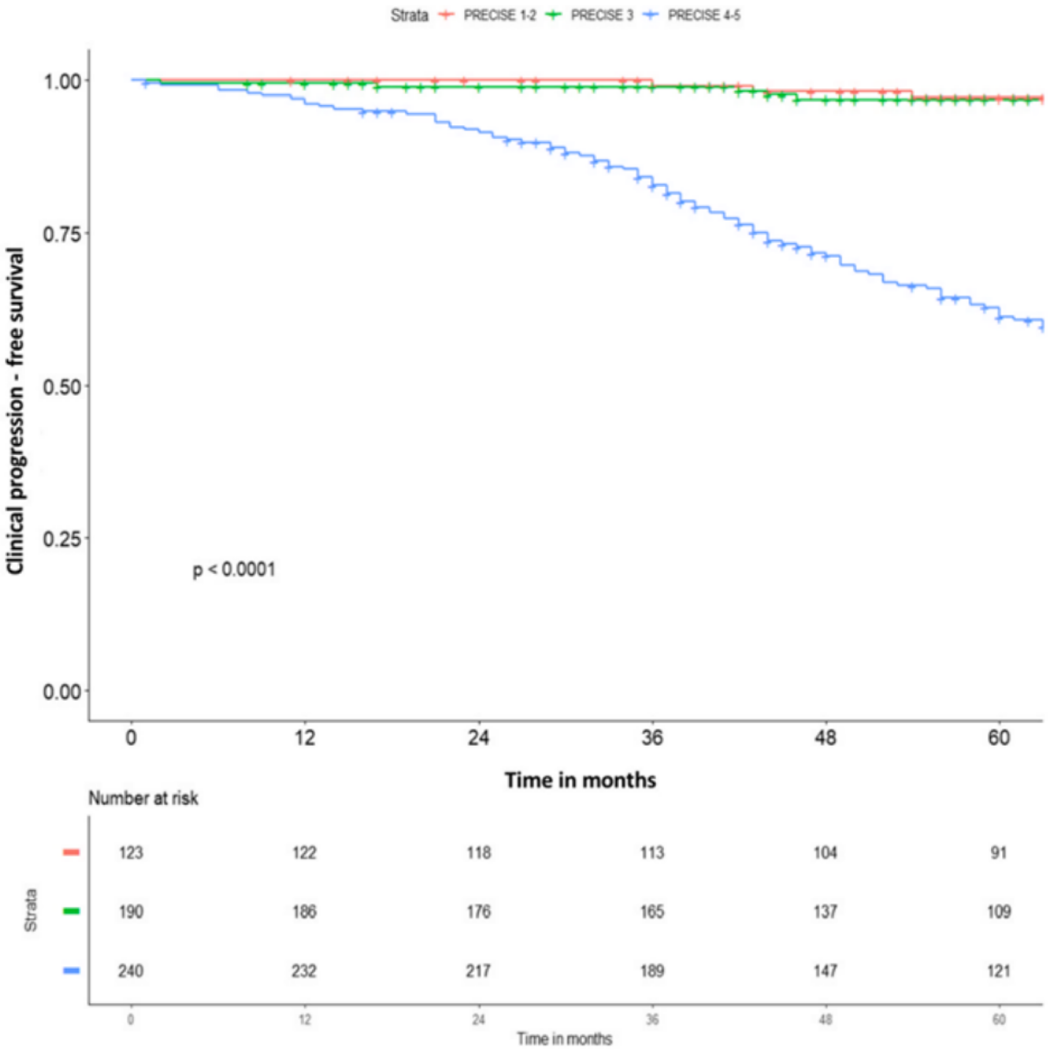
Freedom from clinical progression was: i) 100% at 12 and 24 months and 97% at 60 months for PRECISE 1 and 2; ii) 99% at 12 and 24 months and 97% at 60 months for PRECISE 3; iii) 96%, 91% and 61%, respectively for PRECISE 4 and 5.

The proportion of men who were free of clinical progression at 12, 24 and 60 months is shown in Fig. 18a (next page). A significant difference ($p < 0.001$) in clinical progression between PRECISE 1 - 2 vs 4 - 5 and PRECISE 3 vs 4 - 5 was observed.

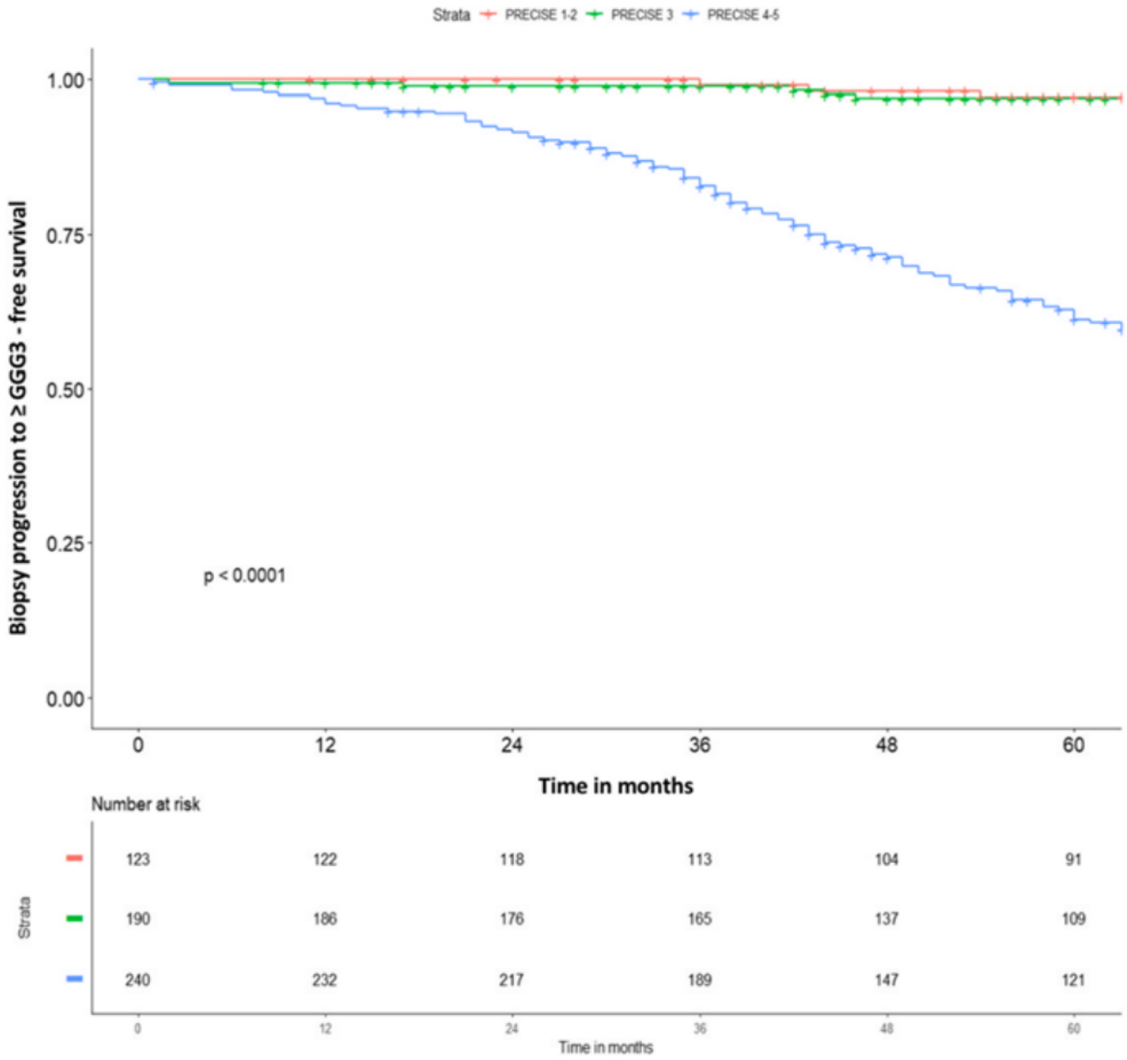
The proportion of patients free from histological progression to ≥ GGG 3 or initiation of active treatment is shown in Fig. 18b (next page) and 18c (next page), respectively.

Fig. 18 *- Kaplan-Meier curves showing the rate of clinical progression (≥ Gleason Grade Group 3 and initiation of active treatment) (a), only biopsy progression (≥ Gleason Grade Group 3) (b) and only initiation of active treatment (c) stratified by PRECISE score (1 - 2 vs 3 vs 4 - 5). Reprinted with permission from [3]*

(a)



(b)


Strata PRECISE 1-2 PRECISE 3 PRECISE 4-5
Biopsy progression to ≥ GGG3 - free survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Time in months
Number at risk
Strata
123 122 118 113 104 91
190 186 176 165 137 109
240 232 217 189 147 121
0 12 24 36 48 60
Time in months

(c)

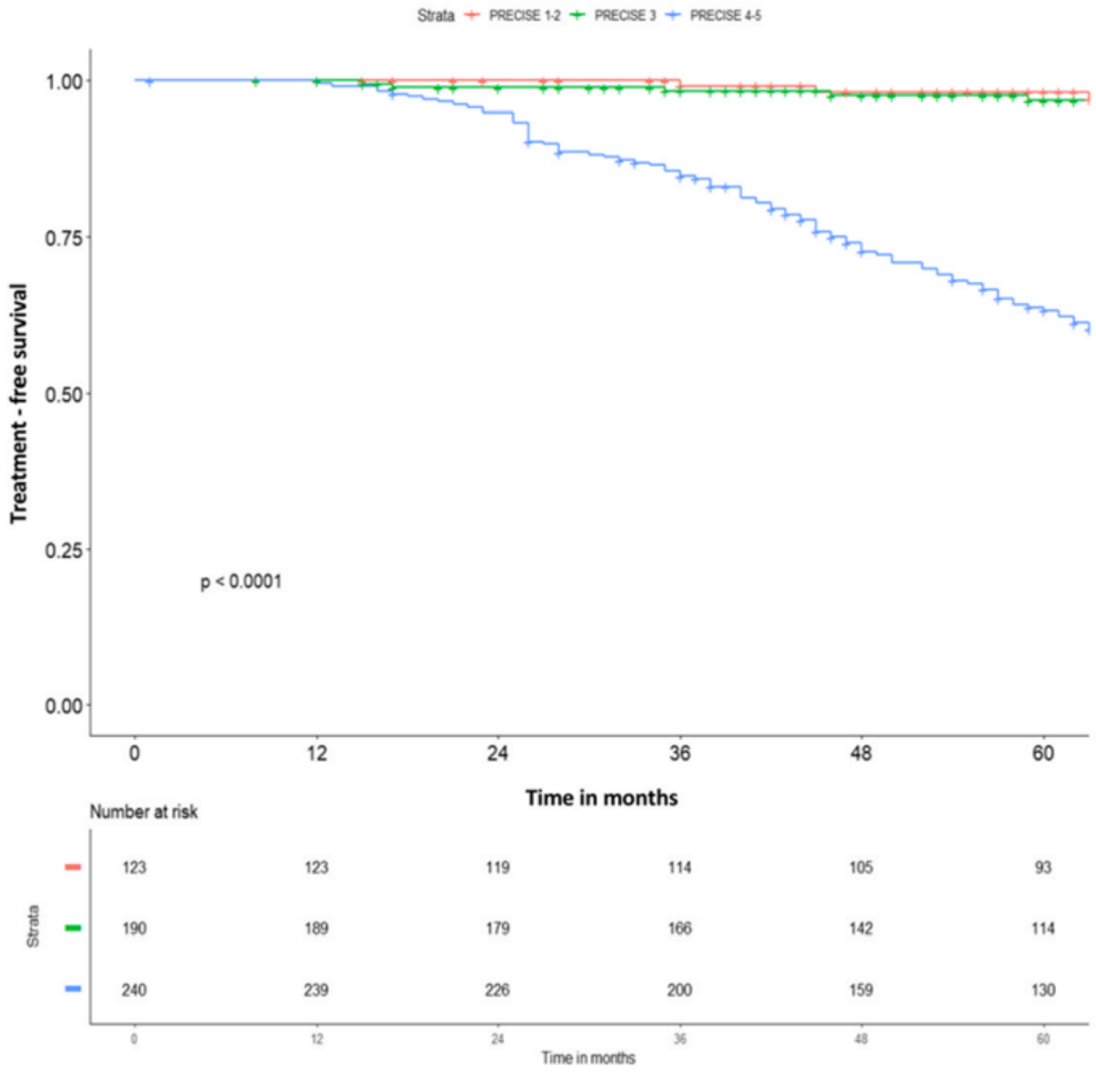

Strata PRECISE 1-2 PRECISE 3 PRECISE 4-5
Treatment - free survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Time in months
Number at risk
123 123 119 114 105 93
190 189 179 166 142 114
240 239 226 200 159 130
Strata
Time in months

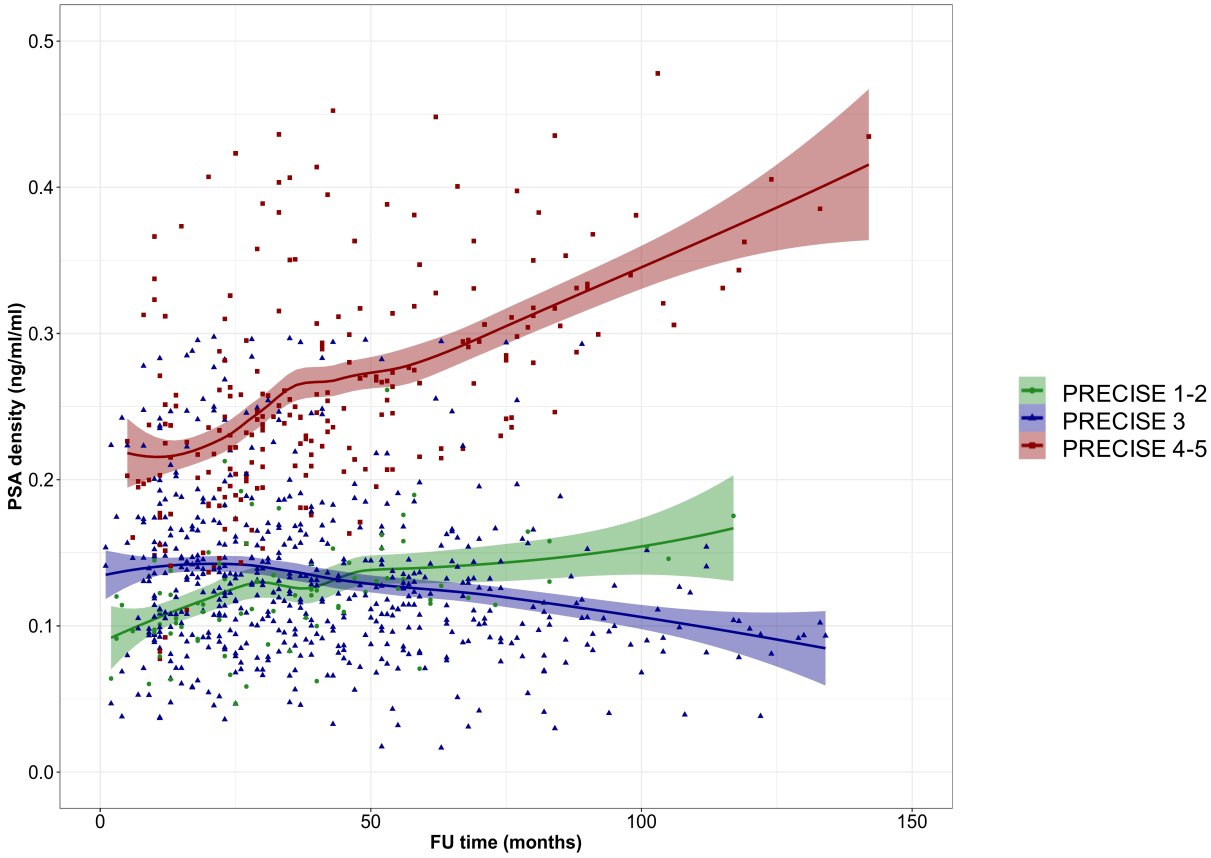
Table 30 shows the number of patients with biopsy progression (defined as ≥ Gleason 4+3 upgrade) stratified according to a negative or stable MR scan or radiological progression before biopsy.

Table 30 *- Number of patients with biopsy progression (n=129) who had a negative MR or showed MR progression before biopsy. Reprinted with permission from [3]*

	Number of patients	Number of patients with ≥ Gleason 4+3 upgrade
Negative or stable MR before biopsy	44	7
MR progression before biopsy	85	18
Total	129	25

A relationship between change in PSA density and the PRECISE score was observed. More in detail, the interaction term between the PRECISE score and each follow-up mpMRI in predicting PSA density variation over time was significant for PRECISE 4 - 5 (hazard ratio 1.04; p =0.01), as shown in Fig. 19.

Fig. 19 *- Relationship between each follow-up MRI and PSA density over time stratified by PRECISE score (1–2vs 3 vs 4–5) in the overall population.*



Legend - PSA, prostate specific antigen; FU: follow-up. Reprinted with permission from [3]

In accordance with the PRECISE case report form, the parameters used to assess the PRECISE score for each patient are reported in Table 31 (next page).

Table 31 *- Parameters used to assess the PRECISE score for each patient included in the study according to the PRECISE case report form.*

	PRECISE 1 (n=100)	PRECISE 2 (n=23)	PRECISE 3 without lesion (n=152)	PRECISE 3 with visible lesion (n=38)	PRECISE 4 (n=211)	PRECISE 5 (n=29)
PSA (ng/ml)	6.60 [4.68-9]	7 [3.6-11]	6.4 [3.82-9.61]	6.53 [4.05-10]	7.40 [5.17-10]	9 [7.1-13.36]
PSA density (ng/ml/ml)	0.11 [0.07-0.16]	0.11 [0.07-0.19]	0.11 [0.07-0.15]	0.09 [0.07-0.14]	0.15 [0.1-0.23]	0.22 [0.10-0.40]
Prostate volume on T2-WI (cc)	54.45 [42.60-74]	53.63 [39.96-67.14]	52.66 [36.59-73.26]	68.91 [32.86-82.93]	43.84 [33.19-63.75]	40.23 [29.79-69.95]
Magnet strength						
1.5T	76	16	129	32	164	22
3T	24	7	23	6	47	7
Likert score						
1-2	100	-	132	-	-	-
3	-	21	20	13	43	2
4	-	2	-	23	114	9
5	-	-	-	2	54	18
PI-RADS score						
1-2	100	2	146	-	-	-
3	-	20	6	14	40	2
4	-	1	-	22	137	16
5	-	-	-	2	34	11
T3a – T3b	-	-	-	-	-	29
Single max diameter (cm) at follow up	-	0.77 [0.60-1.23]	-	0.82 [0.66-1.23]	0.92 [0.67-1.38]	1.37 [1.01-2.28]
Biaxial measurement (cm) at follow up	-	0.73 [0.38-1.05]	-	0.75 [0.5-1.12]	0.77 [0.44-1.27]	1.22 [0.84-2.49]
Lesion volume (ellipsoid formula) on T2-WI (cc) at follow up	-	0.12 [0.10-0.19]	-	0.23 [0.14-0.33]	0.22 [0.11-0.54]	0.45 [0.24-1.57]

Lesion volume (planimetry) on T2-WI (cc) at follow up	-	0.14 [0.09-0.21]	-	0.21 [0.13-0.29]	0.23 [0.12-0.49]	0.45 [0.23-1.1]
Sequence where lesion best seen:	-	11	-	10	63	12
T2-WI	-	5	-	11	70	6
DWI	-	7	-	17	78	11
DCE						
Lesion volume (where lesion best seen)	-	0.15 [0.12-0.27]	-	0.21 [0.16-0.37]	0.30 [0.15-0.56]	0.68 [0.26-1.59]
ADC min ($\times 10^{-3}$ mm^2/s)	-	0.42 [0.22-0.74]	-	0.48 [0.32-0.69]	0.47 [0.26-0.64]	0.40 [0.27-0.53]
ADC mean ($\times 10^{-3}$ mm^2/s)	-	0.89 [0.81-1.10]	-	0.84 [0.70-0.97]	0.84 [0.69-0.99]	0.80 [0.71-0.98]
ADC median ($\times 10^{-3}$ mm^2/s)	-	0.91 [0.80-1.12]	-	0.86 [0.70-1.01]	0.83 [0.67-1]	0.79 [0.71-0.95]
Lesion location						
Right peripheral zone	-	9	-	16	100	10
Left peripheral zone	-	13	-	14	82	14
Right transitional zone	-	1	-	4	15	3
Left transitional zone	-	-	-	4	14	2
Parameters changed from previous scan:						
Dimensional criteria	-	12	-	-	62	-
Conspicuity:						
T2-WI	-	4	-	-	5	-
DWI	-	1	-	-	2	-
DCE	-	2	-	-	1	-
New lesion	-	-	-	-	141	-
PI-RADS score	-	4	-	-	-	-
Stage progression	-	-	-	-	-	29

Data are medians with interquartile ranges in brackets. Reprinted with permission from [3]

5.3.2 Secondary Outcome – relationship between tumour measurements and PRECISE score

This subcohort comprised 196 patients with a visible lesion scoring PI-RADS ≥ 3; ii) two mpMRI scans (baseline and follow-up, with the latter being the most recent if multiple scans had been performed over the years) and iii) diagnosis of prostate confirmed exclusively by targeted biopsy, for a total of 392 scans acquired between December 2005 and November 2019.

The median interval between baseline and follow-up mpMRI was 36 months [22.25 - 52.50]. Overall, 274/392 (70%) scans were conducted on a 1.5T and 118/392 (30%) on a 3T scanner.

Table 32 (next page) reports baseline characteristics of this subcohort. Twenty-four out of 196 (12%) patients were scored as PRECISE 2 (i.e., reduction of suspicious MR features), 41/196 (21%) as PRECISE 3 (i.e., stable MR findings), 116/196 (59%) as PRECISE 4 (i.e., MR progression) and 15/196 (8%) as PRECISE 5 (i.e., stage progression).

Table 32 *- Baseline characteristics of the cohort with exclusively targeted biopsy (n=196)*

Age (years)	63 (58-67)
PSA (ng/ml)	6.5 (4.9-9.06)
Prostate volume (cc)	43.1 (32.1-61.7)
PSA density (ng/ml/ml)	0.14 (0.1-0.19)
Gleason score at entry biopsy	
3+3	155 [79]
3+4	41 [21]
Imaging field strength	
1.5T	140 [71]
3T	56 [29]
Lesion location	
Peripheral zone	160 [82]
Transitional zone	36 [18]
PI-RADS	
3	62 [32]
4	124 [63]
5	10 [5]

Legend: Data are medians and interquartile range (parentheses); percentages in brackets [%]. PSA= Prostate Specific Antigen; PI-RADS: Prostate Imaging-Reporting and Data System.
Reprinted with permission from [10].

Table 33 reports the Spearman's correlation coefficients among the different measurements at baseline and follow-up scans. Assuming tumour volume by planimetry as the reference standard, the ellipsoid formula showed the highest correlation both at baseline (ρ = 0.97 [0.96 - 0.98]) and follow- up (ρ = 0.98 [0.97-0.98]) imaging, followed by the biaxial measurement and, lastly, by the single maximum diameter.

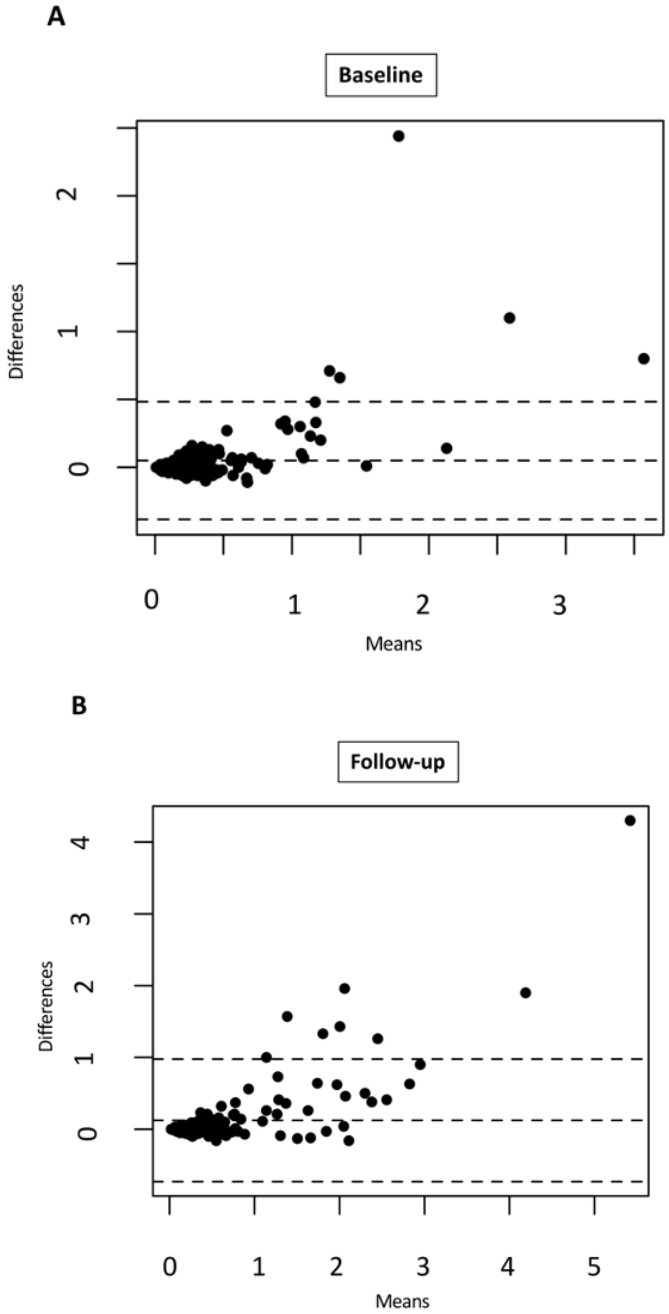
Table 33 *- Spearman's correlation coefficients among the different measurements.*

	Baseline mpMRI				Follow up mpMRI			
	Planimetry	Ellipsoid	Biaxial	Maximum diameter	Planimetry	Ellipsoid	Biaxial	Maximum diameter
Planimetry	1	0.97 [0.96-0.98]	0.88 [0.84-0.92]	0.85 [0.80-0.90]	1	0.98 [0.97-0.98]	0.88 [0.83-0.93]	0.87 [0.82-0.92]
Ellipsoid	0.97 [0.96-0.98]	1	0.87 [0.83-0.92]	0.86 [0.81-0.91]	0.98 [0.97-0.98]	1	0.88 [0.83-0.93]	0.88 [0.83-0.93]
Biaxial	0.88 [0.84-0.92]	0.87 [0.83-0.92]	1	0.94 [0.92 – 0.96]	0.88 [0.83-0.93]	0.88 [0.83-0.93]	1	0.96 [0.95-0.98]
Maximum diameter	0.85 [0.80-0.90]	0.86 [0.81-0.91]	0.94 [0.92 – 0.96]	1	0.87 [0.82-0.92]	0.88 [0.83-0.93]	0.96 [0.95-0.98]	1

Legend – Interquartile ranges in brackets. MpMRI: multiparametric magnetic resonance imaging. Reprinted with permission from [10].

The relationship between tumour volume by planimetry and the ellipsoid formula at each time point is corroborated by the Bland–Altman plots in Figure 20.

Figure 20 *- Bland–Altman plots showing the relationship between tumour volume by planimetry and by the ellipsoid formula both at baseline (a) and at follow- up imaging (b). The centre line is the mean of the differences and the top and bottom lines represent the limits of agreement (± 1.96 times the standard deviation). Reprinted with permission from [10].*



The median values for the four different measurements at each time point stratified by PRECISE score are shown in Table 34.

Table 34 *- Median values according to the four different measurements at baseline and follow-up scans stratified by radiological regression/stability (PRECISE 2 and 3) and radiological progression (PRECISE 4 and 5).*

	PRECISE score 2-3 (n=65)	PRECISE score 4-5 (n=131)	*p*
Baseline mpMRI			
Planimetry (cc)	0.17 [0.12 - 0.33]	0.18 [0.1 - 0.31]	0.50
Ellipsoid formula (cc)	0.16 [0.12 - 0.41]	0.17 [0.09 - 0.33]	0.51
Biaxial (mm^2)	0.68 [0.38 - 1.27]	0.62 [0.44 - 1]	0.48
Maximum diameter (mm)	1 [0.69 - 1.34]	0.90 [0.68 - 1.17]	0.40
Follow-up mpMRI			
Planimetry (cc)	0.17 [0.10 - 0.29]	0.40 [0.20 - 0.70]	< 0.001
Ellipsoid formula (cc)	0.18 [0.09 - 0.29]	0.44 [0.19 - 0.78]	< 0.001
Biaxial (mm^2)	0.73 [0.38 - 1.01]	1.07 [0.71 - 0.81]	< 0.001
Maximum diameter (mm)	0.53 [0.62 - 1.15]	1.17 [0.86 - 1.73]	< 0.001

Legend: Data are medians with interquartile ranges in brackets. MpMRI: multiparametric magnetic resonance imaging.

Reprinted with permission from [10].

Table 35 shows the average yearly percentage volume change between baseline and follow- up scans stratified by radiological regression/stability (i.e., PRECISE 2 and 3) and radiological progression (i.e., PRECISE 4 and 5) for the four different measurements. In particular, for planimetry and for the ellipsoid formula patients with radiological regression (i.e., PRECISE 2 and 3) showed a reduction in size over time (- 3.51% and - 3.06%, respectively) compared to a significant increase in size (36.13 and 43.72%, respectively) for patients with radiological progression (i.e., PRECISE 4 and 5), with a difference between groups of 39.64% and 46.78%, respectively.

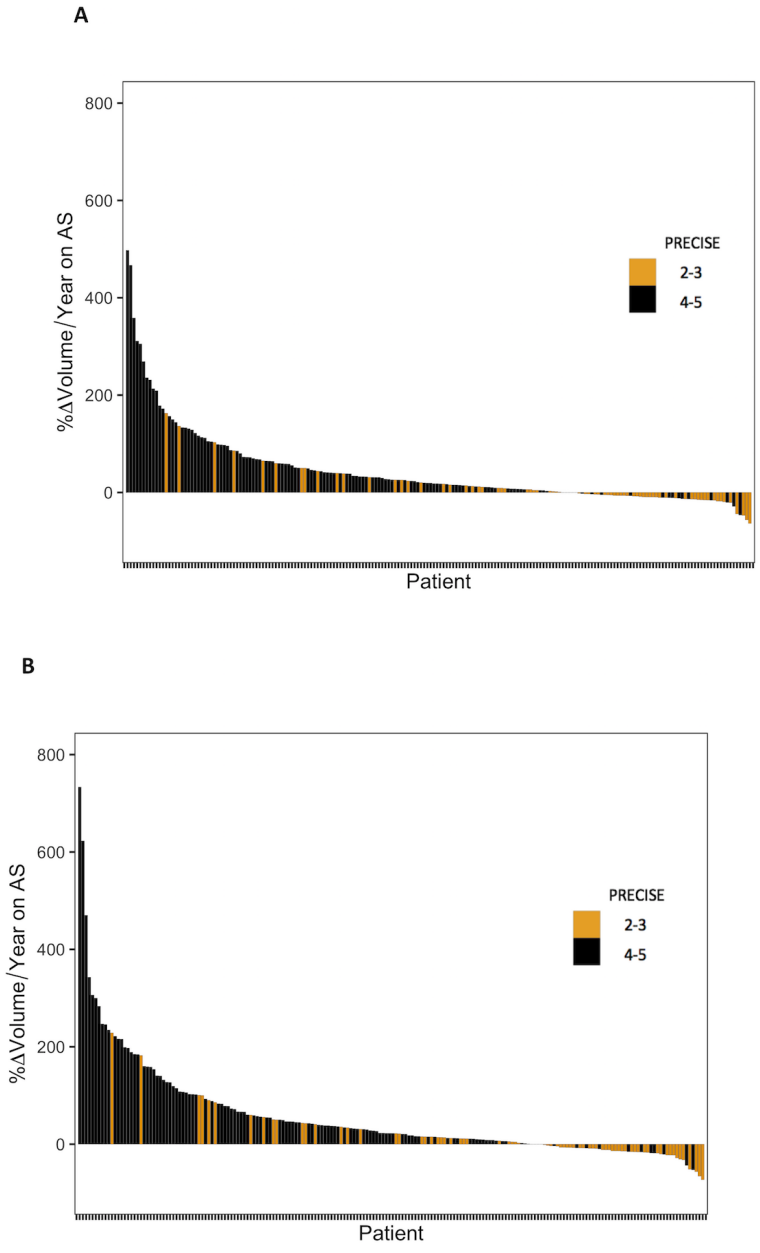
Table 35 *- Average yearly percentage volume change between baseline and follow up scans stratified by radiological regression/stability (PRECISE 2 and 3) and radiological progression (PRECISE 4 and 5). Reprinted with permission from [10].*

Volume definition	PRECISE score 2-3 (n=65)	PRECISE score 4-5 (n=131)	*p*
Planimetry (%)	- 3.51 [- 10.45 – 13.02]	36.13 [11.83 – 89.07]	< 0.001
Ellipsoid formula (%)	- 3.06 [- 14.28 – 15.36]	43.72 [15.19 – 109.64]	< 0.001
Biaxial (%)	-0.54 [-7.50 – 15.77]	24.28 [7.42 – 53.29]	< 0.001
Maximum diameter (%)	0.06 [-8.31 – 10.69]	12.90 [3.73 – 25.59]	< 0.001

Legend – Data are medians with confidence intervals in brackets. Analysis of variance (Kruskal-Wallis test) is p=0.76 and p<0.001 for PRECISE 2-3 and PRECISE 4-5, respectively.

The waterfall plots in Figure 21 show the growth rate expressed in years for the ellipsoid formula and for planimetry, stratified by each PRECISE score and by subgroup (PRECISE 2 and 3 *vs* PRECISE 4 and 5). Some scans were scored as PRECISE 4 because of the increased conspicuity but any increase in size.

Figure 21 *- Waterfall plot showing the different tumour growth rate per year (expressed as percentage) according to PRECISE score (PRECISE 2–3 vs PRECISE 4–5) for tumour volume by planimetry (a) and by ellipsoid formula (b). Reprinted with permission from [10].*



5.4 Discussion

My work has shown that radiological stability is associated with 97% freedom from clinical progression at 5 years and has demonstrated that a PI-RADS score of 4 or 5 at entry to AS is correlated with PRECISE 4 or 5 in up to 68% at a median of 5 years. In other words, more than 2/3 of visible lesions on mpMRI will increase in size, conspicuity or stage over a 5-year period. [3]

Another important result of the work presented in this chapter is that an increase in PSA density over time is significantly associated with radiological progression (i.e., PRECISE 4 - 5). [3]

In addition to this, I found that the ellipsoid formula is the method with the highest correlation at baseline and follow-up imaging ($\rho = 0.97$ and $\rho = 0.98$, respectively) and that the average yearly percentage volume change for both measurements (planimetry and ellipsoid formula) is significantly different ($p < 0.001$) according to radiological change expressed by the PRECISE scoring system. [10]

The findings above corroborate what I had previously observed in a preliminary project on this cohort during my one-year fellowship at UCLH in 2015, where 17% of men with no visible lesion on AS developed a visible lesion at a median follow up of 3.6 years, with a significant increase in volume by a median of 10% ($p < 0.01$), in particular by a median of 6% for Gleason 3+3 and 18% for Gleason 3+4 prostate cancer ($p = 0.058$). [11]

We have seen that the definition of radiological progression is challenging and that inclusion criteria for AS differ across the world. In our clinical practice at UCLH, some patients with low-volume Gleason 3+4 at entry (which means that they already meet the criterion for choosing active treatment at baseline if they wish) and who show radiological progression may wish to avoid a biopsy and proceed with active treatment.

The lack of additional biopsy in our cohort should not be seen as a drawback, as it has significant advantages in terms of patient acceptability and compliance.

The risk of missing the opportunity for cure in a timely manner is no higher than standard biopsy alone, as for example 1/553 patients (< 1%) in this cohort developed nodal disease and 2/553 (< 1%) patients had bone metastases whilst on AS, with median follow-up of 6.3 years. These data compare well to the Sunnybrook cohort, where 13/980 (1.3%) patients had nodal involvement, and 18/980 (1.8%) patients showed bone metastases, with a median follow-up of 6.3 years. [12]

As far as the use of PSA kinetics in patients on AS is concerned, it has been reported that PSA kinetics are not predictive for biopsy upgrade. [13]

However, our results reveal an association of change in PSA density with the PRECISE score (i.e., with radiological progression) and should our findings be confirmed in larger cohorts, PSA density could be used as a trigger for further examination rather than a protocol-based approach using time from initial diagnosis.

As far as the sub cohort related to the secondary outcome (that included men whose had a visible lesion scoring PI-RADS ≥ 3 exclusively diagnosed by targeted biopsies) is concerned, it should be highlighted that I deliberately focused this study on data

from T2-WI to ensure the most accurate calculation of each single diameter in the analysis, as T2-WI is the only sequence where two orthogonal planes are acquired.

This has guaranteed consistency in terms of lesion conspicuity for the different measurements and has allowed a detailed visualisation of prostate anatomy and an optimal soft tissue contrast at the same time. This helped me to better distinguish between genuine lesions and partial volume averaging effects and the recommendation from the results is that tumour volume during AS should be recorded using the ellipsoid formula.

However, we know that there is yet no consensus regarding the best method for measuring tumour size in order to distinguish between radiological regression or stability (i.e., PRECISE 1 - 3) and radiological progression (i.e., PRECISE 4 - 5) on AS. During the consensus meeting, the PRECISE working group pointed out that the measurement errors of small lesions could be larger than any change, even if significant in percentage terms. In fact, mpMRI can overestimate tumour volume for small or low-grade disease (a commons scenario during AS) as small lesions are often surrounded by areas of high-grade prostate intraepithelial neoplasia or areas of inflammation/atrophy that can mimic low-grade tumour, resulting in false-positive findings on imaging. [14]

To my knowledge, the results presented in this chapter are the first attempt to compare four different measurement methods of the index lesion in patients with prostate cancer on AS and also to investigate the relationship between tumour growth rate on serial mpMRI and the PRECISE score. I found that the ellipsoid

formula is a good method to assess tumour volume in a cohort of patients with prostate cancer diagnosed by targeted biopsy. It is known that contouring lesions by planimetry is the most accurate method to define imaging-based volume of prostate cancer, but we have seen that this method is time consuming, especially during daily clinical practice.

5.4.1 Limitations

A limitation of the results presented in this chapter is that entry biopsy in our cohort at UCLH was often TRUS-guided and without a clear definition of the lesion location.

In addition to this, we have stated that our population strongly relies on mpMRI findings therefore not all patients underwent re-biopsy during follow-up and resampling was often triggered by apparent tumour growth on mpMRI. This means that patients with a negative scan did not routinely undergo biopsies and this could contribute to verification bias. However, the likelihood of clinically significant prostate cancer with negative mpMRI is low and such patients are unlikely to benefit from a biopsy. [15] Also, all patients entering AS at UCLH with an external diagnostic biopsy are required to have a concordant mpMRI and biopsy and undergo repeat biopsy to assess any discordance if required, and men with a visible lesion deemed likely to contain Gleason pattern 4 will have an additional MRI-targeted biopsy after referral before a definitive management plan is made.

It is reasonable to observe that I have been the only radiologist applying the PRECISE recommendations in this cohort, and this could represent a limitation.

However, as part of my PhD, I have also investigated the interobserver agreement of the PRECISE score between two expert radiologists in a multicentre study that I carried out with Professor Valeria Panebianco from Sapienza University in Rome. These results will be discussed in the next chapter (Chapter 6).

Another limitation is that some patients received scans on both 1.5T and 3T scanners, and this may have limited the ability to accurately compare measurements of lesions between scans. Again, this is something that has been investigated during my collaboration with the group from Sapienza University in Rome and I will discuss these results in the next chapter (Chapter 6).

Lastly, it is true that mpMRI quality has improved over time, and the earliest scans from 2005 might have been less informative than the most recent ones. The issue of prostate mpMRI quality has represented another aspect of my PhD and the results on this topic will be discussed in Chapter 7.

5.4.2 Conclusions

The results presented in this study suggest that:

- the PRECISE score could identify patients on AS who progress (i.e., PRECISE 4 - 5) in a timely manner, promoting re-biopsy/ treatment

- the PRECISE score could allow avoidance of routine repeat biopsy for patients with radiological regression or stability (i.e., PRECISE 1 - 3),

reducing the burden of surveillance for the individual and the healthcare system

- tumour volumes calculated using the ellipsoid formula are strongly correlated with planimetry based tumour volumes and could be used to monitor tumour growth on mpMRI during AS

- there is a significant difference in the average yearly percentage volume change over time stratified by radiological regression/stability (i.e., PRECISE 2 - 3) and radiological progression (i.e., PRECISE 4 - 5)

- tumour volume using the ellipsoid formula should be recorded in AS cohorts, as this approach is relatively straightforward to implement in a clinical workflow compared to planimetry.

5.5 Related publications

1. Giganti F, Stabile A, Stavrinides V, et al. Natural history of prostate cancer on active surveillance: stratification by MRI using the PRECISE recommendations in a UK cohort. Eur Radiol. (2020) (in press) doi: 10.1007/s00330-020-07256-z.

2. Giganti F, Moore CM, Punwani S, Allen C, Emberton M, Kirkham A. The natural history of prostate cancer on MRI: lessons from an active surveillance cohort. Prostate Cancer Prostatic Dis. (2018); 21(4):556-563.

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5.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study design (publication 1, 2, 3 and 4)
- Acquisition of data: (publication 1, 2, 3 and 4)
- Statistical analysis: (publication 1, 2, 3 and 4)
- Interpretation of data and writing (publication 1, 2, 3 and 4)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1, 2 and 4): in particular, Professor Moore contributed to the study design, data interpretation and obtained funding for publication n. 1
- Dr Armando Stabile (publication n. 1)
- Dr Alex Kirkham (publication n. 2)
- Dr Vasilis Stavrinides (publication n. 3)

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Chapter 6 Interobserver reproducibility of the PRECISE scoring system: the BRACCO fellowship

In this chapter I present the results from a 2-month fellowship, awarded in 2019 by the European School of Radiology (Bracco fellowship) and by the UCL Erasmus+ programme.

The findings presented in this chapter have been published in *European Radiology* [9] and in *Magnetic Resonance Imaging* [10].

6.1 Introduction

In the previous chapter I reported the results from the application of the PRECISE recommendations in our cohort at UCLH.

The PRECISE criteria are still relatively new in the radiological community and formal exploration of the inter-reader reproducibility of the PRECISE criteria are needed to assess whether such recommendations can be used in clinical practice. During the second year of my PhD, I was awarded the Bracco clinical fellowship (endorsed by the European School of Radiology) and obtained additional funding from the UCL Erasmus+ programme.
The BRACCO fellowship, which is specifically devoted to the professional and scientific development of young radiologists in another European training centre, took place in May and June 2019 at Sapienza University in Rome under the supervision of Professor Valeria Panebianco, who was one of the panellists of the PRECISE working group. The aims of my fellowship were:

i) to investigate the interobserver reproducibility of the PRECISE score
ii) to evaluate the inter-reader reproducibility of different ADC calculations in relationship to the PRECISE score

with two experienced prostate MRI radiologists who had been using the PRECISE recommendations in daily clinical practice since their publication in 2017, using images from different MR scanners and patient cohorts (UCLH and Sapienza).

6.2 Materials and Methods

6.2.1 Patient population

Eighty patients (40 from each centre) were randomly selected according to the following criteria: (i) low- or intermediate-risk prostate cancer on AS (i.e., ≤ Gleason 3+4 and PSA ≤ 20 ng/ml); (ii) two or more prostate MR scans conducted between April 2006 and May 2019.

An additional criterion was applied for the evaluation of the inter-reader reproducibility of the ADC, which included only those patients who had been consecutively scanned on the same MR system (i.e., same magnet strength and same MR protocol including the same *b* values for each patient) both for baseline and follow-up scans (i.e., no other scans between them).

Patients who had any treatment with any 5-alpha reductase inhibitors in the previous 12 months were excluded, as we have seen in Chapter 3 that the use of such medications could reduce the conspicuity of prostate cancer on DWI. [1]

6.2.2 Primary aim

The primary aim of the work presented in this chapter was to investigate the interobserver reproducibility of the PRECISE score between me and Professor Panebianco, using scans from the two cohorts.

6.2.3 Secondary aim

The secondary aim was to investigate the correlation of DWI with radiological progression and see if DWI can be used to differentiate patients with radiological progression from those showing stable disease on mpMRI. In order to do this, I evaluated the inter-reader reproducibility of different ADC calculations from serial mpMRI and then explored if they were related to the PRECISE score.

6.2.4 MR protocol

At UCLH, three different scanners were used: two 1.5T (Symphony or Avanto, Siemens) and one 3T (Achieva, Philips) MR system, with a pelvic phased-array coil. The multiparametric protocol comprised T2-WI, DWI (including high *b* value sequences: 1,400 s/mm^2 for 1.5T or 2,000 s/mm^2 for 3T scanners) and DCE imaging
At Sapienza, all exams were performed on a 3T scanner (Discovery MR750, GE Healthcare) using a 32-multichannel surface phased-array body coil, but in some of the earlier scans an endorectal coil was also used.
In a similar way to UCLH, the mpMRI protocols at Sapienza included T2-WI, DWI (*b* values, 0, 100, 500 and 1000 s/mm^2, and high *b* sequence of 2000 s/mm^2) and DCE imaging, as per international guidelines. [2]

6.2.5 MR analysis and PRECISE score assessment

For the primary outcome, Professor Panebianco and I scored each scan according to PI-RADS v.2.1 guidelines [3] and assessed the PRECISE score from the second

scan onwards independently, considering any change in size (according to the maximum diameter) or conspicuity (on any MRI sequence) of the lesion.
The lesion diameters were measured on the ADC map for the peripheral zone and on T2-WI for the transition zone as per PI-RADS v. 2.1 guidelines but if the measurement was difficult on these sequences, the lesion was measured on the sequence that showed it best.
We applied the PRECISE score on a per-patient analysis (i.e., overall PRECISE score) and on a per-scan analysis (i.e., a single PRECISE score for each follow-up scan).

For the secondary outcome, Professor Panebianco and I independently obtained median ADC values of the index lesion from ROIs positioned on the ADC map making reference to the most conspicuous focus on the high *b*-value sequence.
In order to minimise the variability between MR systems, we also independently normalised the ADC copying and pasting another ROI of the same size in the non-cancerous peripheral zone or transitional zone (according to tumour location) on the same slice in mirror position, and another region of interest in the urine in the bladder lumen, in a similar fashion to the methodology seen in chapter 3.
These values were used to generate two parameters: the normalised prostatic ADC (npADC; normalised to non-cancerous prostatic tissue) and the normalised urinary ADC (nuADC; normalised to urine in the bladder) ratios, according to the formula: ADC (tumour)/ ADC (reference).

The normalisation of the ADC is an established method that has been previously described [4] and is important in order to minimise the variability between MR

scanners and systems. As far as this study is concerned, the npADC is more discriminating than the single ADC value from the lesion, as one advantage of using the ADC from the non-cancerous prostate as reference is that measurements are made easier with ROIs used for calculation placed on the same level of slice and because it is assumed that the adjacent tissue is subjected to the same field heterogeneity and susceptibility effects than the lesion. Necrosis, blood vessels, and areas containing artefacts from bowel peristalsis were excluded from the ROIs.

6.2.6 Statistical analysis

Clinical and demographic data are shown using descriptive statistics. Continuous variables are summarised by medians and interquartile ranges and categorical variables by frequencies and percentages. Inter-reader agreement was evaluated by the percent agreement and Cohen's kappa with standard quadratic weighting (κw). Kw coefficients were interpreted as follows: 0.01 - 020: slight agreement; 0.21 - 0.40: minimal agreement; 0.41 - 0.60: moderate agreement; 0.61 - 0.80: substantial agreement; 0.81 - 0.90: strong agreement; > 0.90: almost perfect agreement. Spearman's correlation and intraclass correlation coefficients were used to analyse the agreement in measuring ADC values and graphically depicted by Bland-Altman plots. ADC measurements were averaged between the two observers and differences in ADC values and ratios between scans were tested by the Kruskal-Wallis test. Receiver operating characteristic curves were generated to differentiate between PRECISE 2 - 3 and PRECISE 4 - 5. To detect a difference of the median change, an unpaired t-test was carried out. P values < 0.05 were considered to indicate a significant difference.

6.3 Results

6.3.1 Primary aim

Professor Panebianco and I assessed a total of 80 baseline scans using PI-RADS v. 2.1 guidelines and 179 follow-up scans using the PRECISE criteria. Baseline and follow-up characteristics of the entire population are reported in Table 36.

Table 36 *- Descriptive statistics of the patients included in the study for each group.*

	UCLH (n=40)	**Sapienza (n=40)**
Age (years)	63 (56-68)	65 (60-71)
PSA (ng/ml)	6.19 (4.15-8.81)	4.4 (2.14-6.57)
Prostate volume (cc) *	43.64 (31.8-63.38)	48.5 (32-68)
PSA density at baseline	0.12 (0.08-0.18)	0.08 (0.06-0.14)
Gleason score at entry		
3+3	33 [82]	37 [92]
3+4	7 [18]	3 [8]
Biopsy type at entry		
Systematic	36 [90]	37 [92]
Systematic + targeted	0	2 [5]
Targeted alone	4 [10]	1 [3]
Number of MR scans (n=259)	151 [58]	108 [42]
Outcome		
No treatment	28 [70]	37 [92]
Active treatment	12 [30]	3 [8]
Treatment		
Radical prostatectomy	3 [26]	1 [33]
EBRT	1 [8]	1 [33]
Focal therapy	7 [58]	NA
Hormones	1 [8]	1 [33]

Legend: Data are medians and interquartile range (parentheses); percentages in brackets [%]. Data for prostate volume (and PSA density) were calculated using the values from the original report. UCLH: University College London Hospital; PSA= Prostate Specific Antigen; NA= not applicable; MR = Magnetic Resonance; EBRT = external beam radiotherapy. Reprinted with permission from [9].

The median number of MR scans per patient was 3 (IQR: 2.25 - 5) at UCLH and 2 (IQR: 2 - 3) at Sapienza University.

The median interval between the first and the last scan (in months) was 51 (IQR: 29 - 77) at UCLH and 23 (IQR: 13 - 34) at Sapienza University.

Forty-three out of 80 patients (54%) had at least one additional biopsy: 22/43 (51%) at Sapienza [13 of which (59%) were positive] and 21/43 (49%) at UCLH [17 of which (81%) were positive]. For all studied, 13/43 (30%) and 17/43 (40%) were positive.

Overall, 30/43 (70%) showed cancer, nine of which (30%) showed biopsy progression defined as one step in Gleason score upgrade (including those men with Gleason 3+3 at entry and subsequent Gleason 3+4) according to baseline histology: in detail, seven had Gleason score = 3+4 (one in the Sapienza cohort and 6 in the UCLH cohort) and two had Gleason score 4+3 (both in the UCLH cohort), and 7/9 (%) had an overall PRECISE score ≥ 4.

If we have a closer look at Table 36, it should be noted that PSA density was significantly different between the two groups (0.08 ng/ml/ml at Sapienza University vs 0.12 ng/ml/ml at UCLH) ($p = 0.02$) and this explains the treatment differences between the two cohorts (8% at Sapienza University vs 30% at UCLH).

The number of PRECISE cases on a per-patient and on a per-scan basis is reported in Table 37 (next page).

Table 37 *- Number of PRECISE cases on a per-patient and on a per-scan basis, for each reader in the two different cohorts and in the overall population*

Per-patient						
	UCLH (n=40)		Sapienza (n=40)		Overall (n=80)	
	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
PRECISE 1	3 (7)	3 (7)	3 (7)	2 (3)	6 (8)	5 (5)
PRECISE 2	1 (3)	1 (3)	5 (12)	1 (3)	6 (8)	2 (2)
PRECISE 3	21 (53)	20 (50)	23 (58)	27 (67)	44 (55)	47 (59)
PRECISE 4	10 (25)	11 (27)	8 (20)	10 (27)	18 (22)	21 (28)
PRECISE 5	5 (12)	5 (13)	1 (3)	NA	6 (7)	5 (6)
Per-scan						
	UCLH (n=111)		Sapienza (n=68)		Overall (n=179)	
	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
PRECISE 1	4 (4)	6 (5)	4 (6)	3 (3)	8 (5)	9 (5)
PRECISE 2	1 (1)	1 (1)	6 (9)	1 (1)	7 (4)	2 (1)
PRECISE 3	83 (75)	85 (77)	46 (68)	52 (77)	129 (72)	137 (76)
PRECISE 4	19 (17)	14 (13)	11 (16)	12 (19)	30 (16)	26 (15)
PRECISE 5	4 (3)	5 (4)	1 (1)	NA	5 (3)	5 (3)

Legend – Percentages in brackets (%); UCLH: University College London Hospital; NA: not available.

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Twenty-three out of 80 patients (29%) did not develop any visible lesion (i.e., persistent negative scan) both for me and Professor Panebianco.

The inter-reader reproducibility for each single PRECISE score was substantial both at a per-patient and a per- scan level ($\kappa = 0.71$ and 0.61, respectively), with a high specific agreement rate (63/80 per patient, 79% and 145/179, 81% per scan, respectively), as reported in Table 38 (next page).

Table 38 *– Inter-reader agreement*

	PRECISE score (1 to 5)		**PRECISE 1-3 *vs* PRECISE 4-5**	
	Per-patient			
	k value	Percent agreement (%)	k value	Percent agreement (%)
UCLH (n=40)	0.81 [0.49-1]	80	0.95 [0.86-1]	97
Sapienza University (n=40)	0.55 [0.07-1]	78	0.66 [0.42-0.88]	90
Overall (n=80)	0.71 [0.37-1]	79	0.83 [0.71-0.94]	90
	Per-scan			
	k value	Percent agreement (%)	k value	Percent agreement (%)
UCLH (n=111)	0.70 [0.31-1]	86	0.74 [0.61-0.87]	93
Sapienza University (n= 68)	0.48 [0.07-0.89]	75	0.56 [0.35-0.77]	88
Overall (n=179)	0.61 [0.30-0.93]	81	0.67 [0.56-0.79]	91

Legend - 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–0.90, strong agreement and >0.90 almost perfect agreement; interquartile ranges in brackets [IQR]. UCLH: University College London Hospital. Reprinted with permission from [9].

A stronger agreement (κ = 0.83 per-patient and 0.67 per-scan) was observed when the PRECISE scores were grouped according to the presence of radiological progression (i.e., PRECISE 1 - 3 vs PRECISE 4 - 5) together with a very high specific percent agreement (72/80, 90% and 163/179, 91%, respectively).
In terms of PRECISE score, there were 19 discordant cases between me and Professor Panebianco, specifically 8/19 (42%) in the UCLH cohort and 11/19 (58%) in the Sapienza cohort. (Table 39)

Table 39 *– Overall PRECISE scores (n=80) as assessed by each reader*

		Reader 1							Total
		PRECISE 1	PRECISE 2	PRECISE 3	PRECISE 4	PRECISE 5	PRECISE 1,2 and 3	PRECISE 4 and 5	
Reader 2	PRECISE 1	2	2	1	1	0	-	-	6
	PRECISE 2	1	0	4	1	0	-	-	6
	PRECISE 3	2	0	40	2	0	-	-	44
	PRECISE 4	0	0	2	15	1	-	-	18
	PRECISE 5	0	0	0	2	4	-	-	6
	PRECISE 1,2 and 3	-	-	-	-	-	(52)	(4)	(56)
	PRECISE 4 and 5	-	-	-	-	-	(2)	(22)	(24)
Total		5	2	47	21	5	(54)	(26)	80 (80)

Legend – Data in parentheses show the results according to radiological regression or stability (PRECISE 1,2 and 3) and radiological progression (PRECISE 4 and 5).

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6.3.2 Secondary aim

Professor Panebianco and I conducted a sub analysis on 30 patients (fifteen scanned on 1.5T and fifteen on 3T MR systems) with a baseline and follow-up scan. Baseline and follow-up scans were conducted on the same MR systems.
The median interval between scans was 14 months (IQR: 12 - 18.75).
There were 26/30 (87%) lesions in the peripheral zone and 4/30 (13%) in the transitional zone.

The median size of the ROIs (averaged between the two readers) was 15 mm^2 (IQR: 0.11–0.24) for baseline and 20 mm^2 (IQR 0.14–0.41) for follow-up imaging.

Descriptive characteristics of the 30 patients are reported in Table 40 (next page).

Table 40 *– Descriptive characteristics for each man included in the sub cohort (n=30)*

	Age (years)	MR system	Baseline PSA (ng/ml)	Baseline PSA density	Gleason score at entry	Type of biopsy at entry	Follow-up PSA (ng/ml)	Follow-up PSA density	Gleason score at re-biopsy	Type of biopsy at re-biopsy	Time interval between MR scans (months)	Time on AS * (years)	PRECISE score
1	66	3T	5.2	0.11	3+3	S	3.64	0.07	3+3	S	13	4.09	2
2	69	3T	8.09	0.11	3+3	T	4.57	0.06	-	-	16	2.58	2
3	55	3T	6.07	0.12	3+3	T	8.89	0.18	3+3	T	13	3.08	3
4	61	3T	5.58	0.08	3+4	S	5.18	0.06	-	-	12	4.41	3
5	75	3T	1.95	0.07	3+3	S	1.6	0.03	-	-	14	1.58	3
6	59	3T	0.5	0.01	3+3	S	0.5	0.01	-	-	13	4	3
7	70	3T	9.22	0.22	3+3	T	12.15	0.2	-	-	22	4.92	3
8	62	3T	5.5	0.14	3+4	S	8.01	0.17	-	-	22	8.19	3
9	61	3T	2.93	0.05	3+3	S	3	0.05	-	-	21	12.64	3
10	64	3T	8.8	0.07	3+3	S	11.96	0.09	-	-	16	10.58	3
11	60	3T	7.9	0.17	3+3	S	8.1	0.17	3+4	T	14	7.67	3
12	76	3T	5.63	0.13	3+3	T	9.45	0.19	-	-	18	2	4
13	73	3T	3.23	0.16	3+3	T	2.72	0.15	-	-	11	3.58	4
14	66	3T	1.8	0.06	3+3	S	0.73	0.02	-	-	25	2.75	4
15	64	3T	9.4	0.23	3+4	T	10	0.21	3+4	T	12	12.76	4
16	71	1.5T	6.8	0.07	3+3	S	5.5	0.04	-	-	12	11.61	3
17	61	1.5T	9.4	0.14	3+3	S	11.29	0.13	3+4	S	12	11	3
18	67	1.5T	11.3	0.12	3+3	T	12.8	0.14	3+3	T	23	4.66	3
19	75	1.5T	11.86	0.16	3+3	S	11.4	0.15	3+3	S	21	5.97	3
20	67	1.5T	4.87	0.25	3+3	S	7.7	0.4	-	-	13	7.73	3
21	52	1.5T	7	0.23	3+3	S	12.41	0.34	-	-	16	9.21	4

22	55	1.5T	3.3	0.07	3+3	S	5.2	0.09	-	-	23	7.96	4
23	63	1.5T	6.4	0.2	3+4	S	6.15	0.19	3+4	S+T	13	4.93	4
24	73	1.5T	5.5	0.19	3+3	S	9.4	0.29	3+4	S	12	4.06	4
25	77	1.5T	7	0.14	3+3	S	10.25	0.2	-	-	18	11.79	4
26	62	1.5T	7.5	0.15	3+3	S	9	0.18	3+4	T	12	7.92	4
27	65	1.5T	6	0.08	3+3	S	11	0.14	3+4	T	18	6.03	4
28	50	1.5T	5.4	0.13	3+3	S	5.86	0.14	-	-	12	1.11	5
29	58	1.5T	5.7	0.2	3+4	S	3.38	0.13	-	-	10	1.03	5
30	81	1.5T	10.6	0.11	3+4	S	13	0.12	4+3	T	18	4.52	5
Median (IQR)	65	-	6.03 (5.2-8.09)	0.13 (0.08-0.17)	-	-	8.05 (4.57-11)	0.14 (0.07-0.19)	-	-	14 (12-18.75)	4.9 (3.45-8.44)	-

*Legend – MR: magnetic resonance; PSA: prostate specific antigen; IQR: interquartile ranges; S: systematic; T: targeted. * AS entry was defined as the date of the first positive biopsy.*

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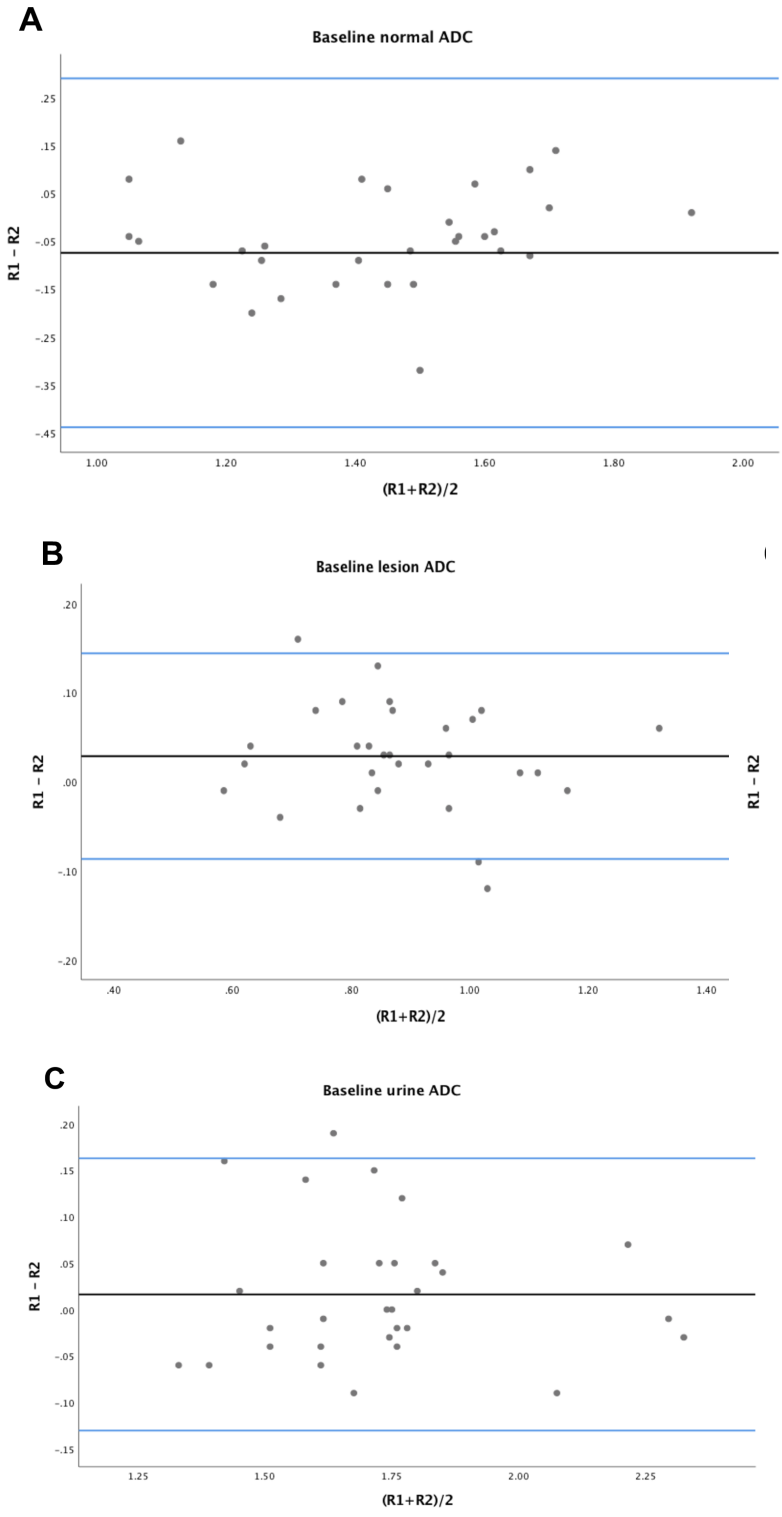
Overall, there were two (6%) PRECISE 2, fourteen (47%) PRECISE 3 (two of which showed pathological progression to Gleason 3+4), eleven (37%) PRECISE 4 (three of which showed pathological progression to Gleason 3+4) and three (10%) PRECISE 5 (one of which showed pathological progression to Gleason 4+3) cases. The fact that 50% of men experienced radiological progression (which may seem quite high) is due to the additional stringent entry criterion applied for this specific study (i.e., only patients who had been consecutively scanned on the same MR system, which means same magnet strength and same MR protocol including the same *b* values for each patient) both for baseline and follow-up scans, with no other scans between them.

At this regard, it should be also noted that biopsies were recommended at the discretion of the treating physician at both institutions. The recommendation was based either on the suspicion of progression on MRI, or on adverse PSA kinetics without MRI changes. Some men, particularly those with GGG 2 disease at the outset of surveillance who could have chosen active treatment, did not wish to have a further biopsy before proceeding to treatment. This was permitted by the treating teams, where GGG 2 disease had previously been established, and therefore some men with radiological progression (i.e., PRECISE 4 or 5) were not re-biopsied before treatment.

The interobserver reproducibility between the two readers was very good both for baseline and follow-up ADC calculations, as graphically displayed in the Bland-Altman plots (Fig. 22) and as shown by the high Spearman's rank and intraclass correlation coefficients (Table 41).

Figure 22 *- Bland-Altman plots representing the interobserver reproducibility between the two readers for the different ADC and normalised ADC ratio values, both at baseline (A, B, C) and at follow-up magnetic resonance imaging (D, E, F). The centre line represents the mean of differences, the top line shows the upper 95% limit of agreement, and the bottom line shows the lower 95% limit of agreement, with the mean difference between the long- and short-axis measurements (±1.96 times the standard deviation). Reprinted with permission from [10].*



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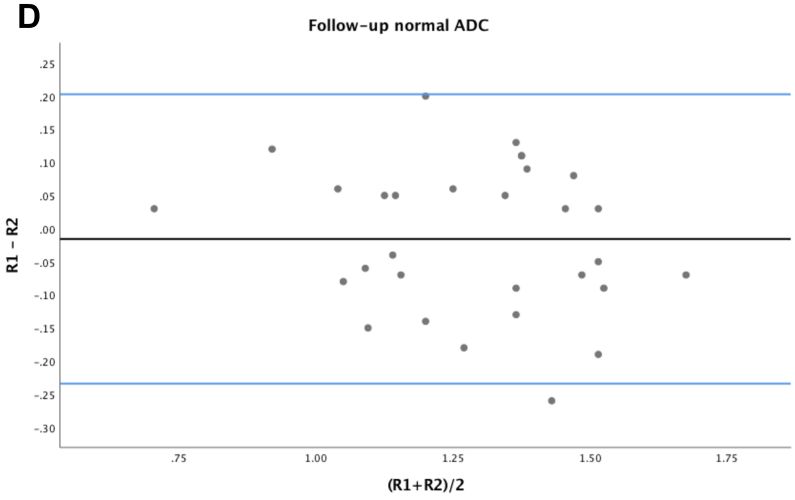
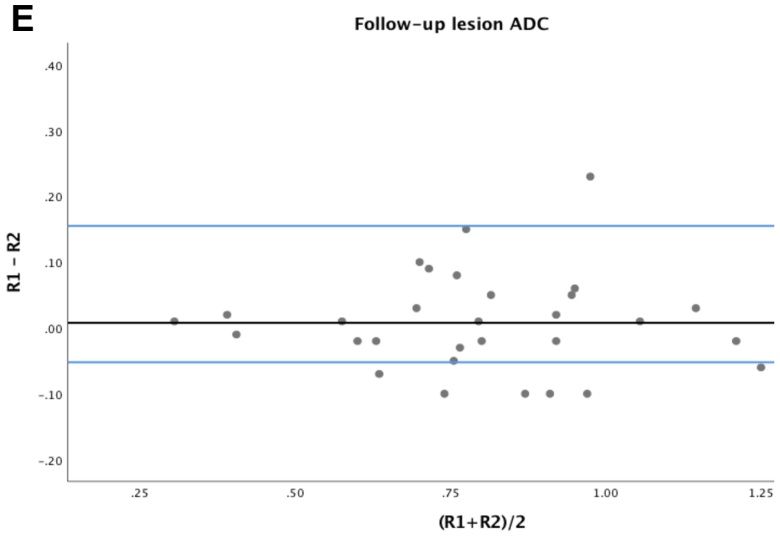

Follow-up normal ADC
R1 - R2
.25
.20
.15
.10
.05
.00
-.05
-.10
-.15
-.20
-.25
-.30
.75
1.00
1.25
1.50
1.75
(R1+R2)/2

E


Follow-up lesion ADC
R1 - R2
.40
.30
.20
.10
.00
-.10
-.20
.25
.50
.75
1.00
1.25
(R1+R2)/2

F

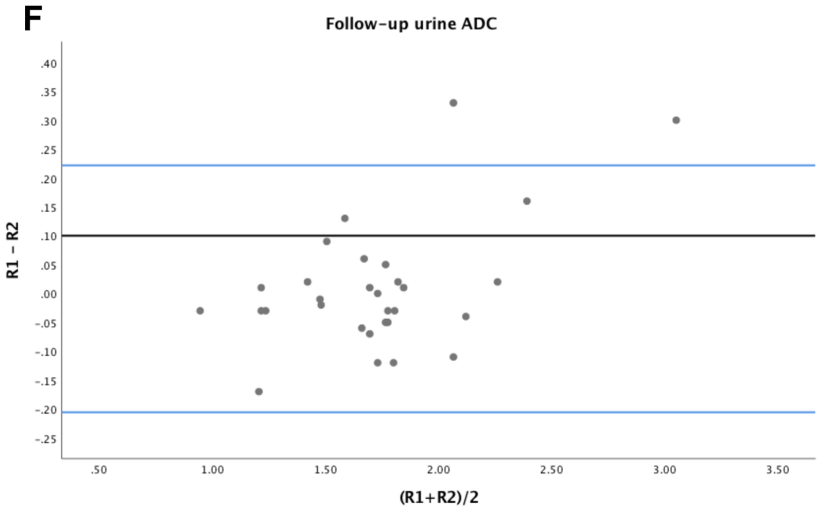

Follow-up urine ADC
R1 - R2
.40
.35
.30
.25
.20
.15
.10
.05
.00
-.05
-.10
-.15
-.20
-.25
.50
1.00
1.50
2.00
2.50
3.00
3.50
(R1+R2)/2

Table 41 *– Spearman's rank correlation coefficients (ρ) and intraclass correlation coefficient at baseline and follow-up mpMRI.*

	Spearman's rho	CI	ICC	CI
Baseline normal ADC	0.871	0.745-0.937	0.926	0.833-0.966
Baseline lesion ADC	0.925	0.847-0.964	0.962	0.907-0.983
Baseline urine ADC	0.887	0.775-0.945	0.976	0.950-0.988
Follow-up normal ADC	0.830	0.671-0.916	0.932	0.857-0.967
Follow-up lesion ADC	0.914	0.826-0.967	0.973	0.943-0.987
Follow-up urine ADC	0.963	0.923-0.982	0.983	0.964-0.992

Legend - CI: confidence intervals; ICC: intraclass correlation coefficient; ADC: apparent diffusion coefficient.

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Table 42 reports the overall median ADC values and normalised ADC ratios stratified by each PRECISE score at baseline and follow-up imaging.

Table 42 *- ADC values (x10^{-3} mm^2/s) and normalised ADC ratios stratified by PRECISE score at baseline and follow-up mpMRI*

		PRECISE 2 (n = 2)	PRECISE 3 (n = 14)	PRECISE 4 (n = 11)	PRECISE 5 (n = 3)
Baseline mpMRI	Normal prostatic tissue ADC	1.36 (1.05-1.67)	1.43 (1.24-1.56)	1.49 (1.29-1.60)	1.26 (1.13-1.63)
	Lesion ADC	0.73 (0.59-0.87)	0.94 (0.86-1.02)	0.82 (0.74-0.97)	0.85 (0.63-1.02)
	npADC	0.54 (0.52-0.56)	0.66 (0.60-0.74)	0.61 (0.51-0.69)	0.63 (0.50-0.75)
	Bladder ADC	1.63 (1.51-1.76)	1.73 (1.61-1.77)	1.75 (1.61-1.22)	1.68 (1.33-1.75)
	nuADC	0.44 (0.39-0.50)	0.55 (0.50-0.58)	0.46 (0.35-0.60)	0.51 (0.47-0.58)
Follow-up mpMRI	Normal prostatic tissue ADC	1.39 (1.27-1.52)	1.30 (1.15-1.38)	1.37 (1.10-1.52)	1.38 (1.16-1.39)
	Lesion ADC	0.97 (0.74-1.21)	0.91 (0.76-0.97)	0.70 (0.60-0.80)	0.80 (0.58-0.87)
	npADC	0.69 (0.58-0.80)	0.68 (0.60-0.78)	0.53 (0.45-0.59)	0.58 (0.42-0.75)
	Bladder ADC	1.74 (1.42-2.07)	1.73 (1.66-1.81)	1.51 (1.22-2.12)	1.78 (1.77-1.82)
	nuADC	0.55 (0.52-0.59)	0.51 (0.44-0.58)	0.36 (0.33-0.53)	0.45 (0.32-0.49)

Legend – Data are medians with interquartile ranges in parentheses. MpMRI: multiparametric magnetic resonance imaging; ADC: apparent diffusion coefficient; npADC: normalised prostatic ADC; nuADC: normalised urinary ADC.

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Splitting the overall population into radiological regression or stability (i.e., PRECISE 2 - 3) and radiological progression (i.e., PRECISE 4 - 5), significant differences were observed for lesion ADC and npADC ratio at follow-up mpMRI (p = 0.025 and p = 0.012, respectively), while there were no differences for all parameters at baseline and for the other values at follow-up imaging (Table 43).

Table 43 *- ADC values (x10^{-3} mm^2/s) and normalised ADC ratios stratified by grouped PRECISE score (i.e., radiological regression/stability vs radiological progression) at baseline and follow-up mpMRI*

		PRECISE 2 and 3 (n = 16)	PRECISE 4 and 5 (n = 14)	*p*
Baseline mpMRI	Normal prostatic tissue ADC	1.43 (1.23-1.58)	1.47 (1.25-1.60)	0.662
	Lesion ADC	0.90 (0.83-1.01)	0.83 (0.75-0.95)	0.163
	npADC	0.64 (0.60-0.73)	0.62 (0.54-0.65)	0.197
	Bladder ADC	1.73 (1.61-1.78)	1.71 (1.58-1.94)	0.803
	nuADC	0.54 (0.49-0.60)	0.48 (0.41-0.48)	0.151
Follow-up mpMRI	Normal prostatic tissue ADC	1.31 (1.21-1.38)	1.37 (1.13-1.44)	0.724
	Lesion ADC	0.91 (0.77-0.99)	0.73 (0.59-0.83)	0.025
	npADC	0.68 (0.60-0.76)	0.53 (0.48-0.63)	0.012
	Bladder ADC	1.74 (1.57-2)	1.73 (1.41-1.90)	0.560
	nuADC	0.52 (0.44-0.57)	0.38 (0.34-0.55)	0.070

Legend – Data are medians with interquartile ranges in parentheses. MpMRI: multiparametric magnetic resonance imaging; ADC: apparent diffusion coefficient; npADC: normalised prostatic ADC; nuADC: normalised urinary ADC. Reprinted with permission from [10].

There were no differences in the change of ADC values between baseline and follow-up scans according to radiological regression or stability (i.e., PRECISE 2 - 3) vs radiological progression (i.e., PRECISE 4 - 5). (Table 44)

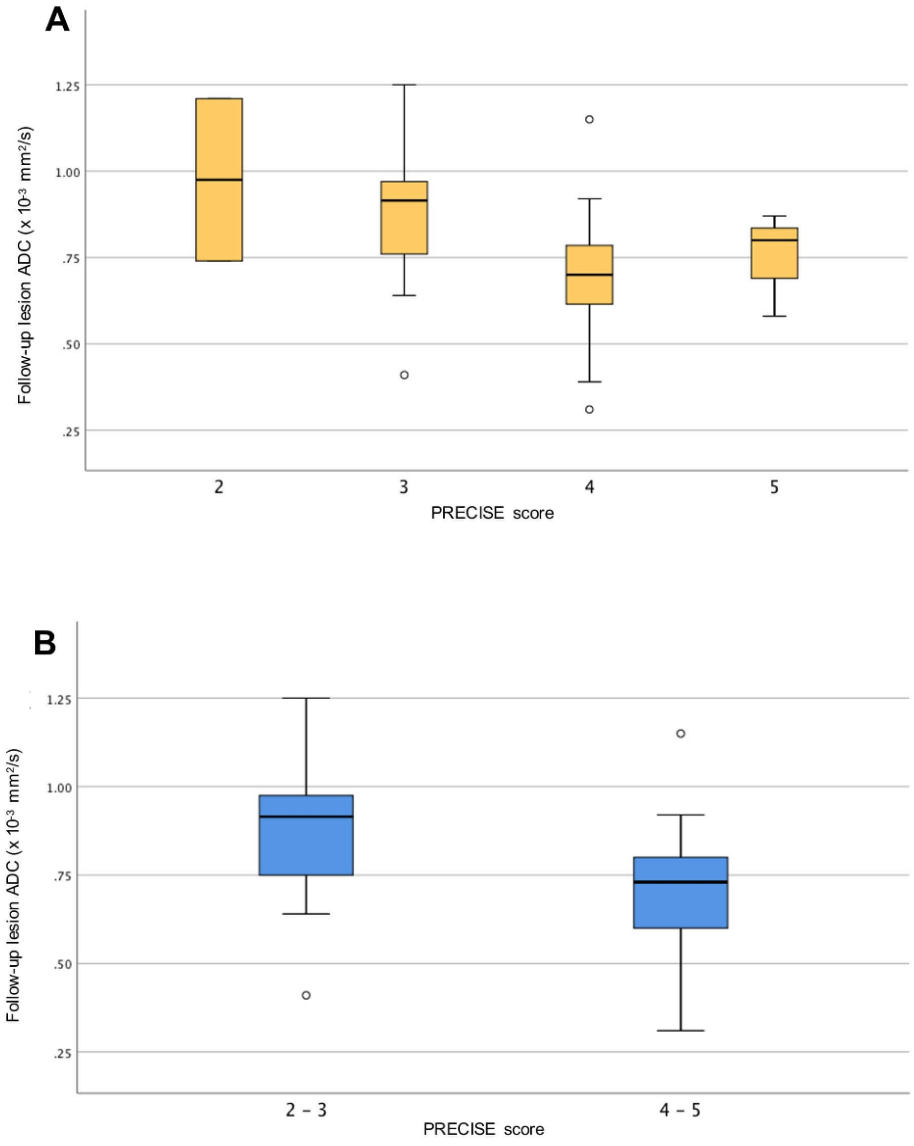
Table 44 *– Differences of the median change of all parameters between baseline and follow-up scans stratified by grouped PRECISE score (i.e., radiological regression/stability vs radiological progression).*

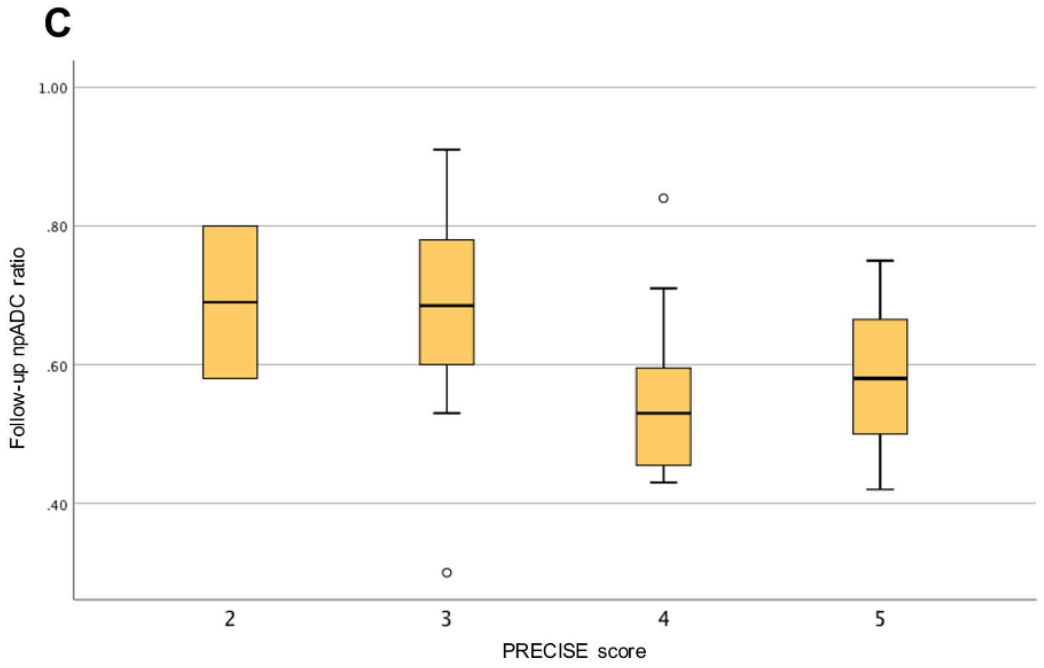
	PRECISE 2 and 3 (n= 16)	PRECISE 4 and 5 (n= 14)	*p*
Δ prostatic tissue ADC	-7.43 (-16.02 — -0.33)	-5.57 (-19.70 — 8.39)	0.81
Δ lesion ADC	-5.39 (-13.87 — 5.78)	-14.79 (-21.02 — -3.22)	0.08
Δ npADC	1.79 (-5.17 — 11.07)	-11.12 (-19.38 — 3.49)	0.14
Δ bladder ADC	-1.53 (-7.15 — 14.42)	-2.71 (-14.43 — 2.79)	0.22
Δ nuADC	-6.52 (-18.97 — 5.93)	-9.95 (-22.79 — -1.05)	0.98

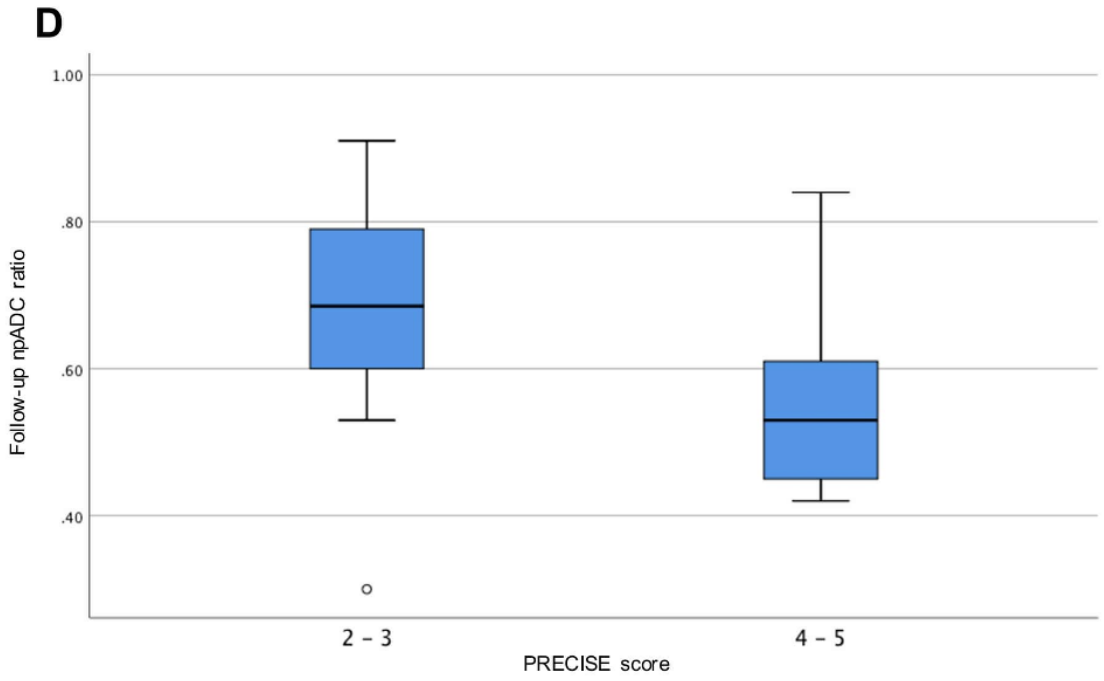
Legend – Data are medians with interquartile ranges in parentheses. ADC: apparent diffusion coefficient; npADC: normalised prostatic ADC; nuADC: normalised urinary ADC.
Reprinted with permission from [10].

The median lesion ADC and npADC ratio for each PRECISE score and according to radiological regression or stability (i.e., PRECISE 2 - 3) vs radiological progression (i.e., PRECISE 4 - 5) at follow-up imaging are graphically displayed in Fig. 23.

Figure 23 - *Boxplots showing lesion ADC (A, B) and normalised prostatic ADC (npADC) values (C, D) at follow-up magnetic resonance imaging as function of each single PRECISE score (A, C) and according to radiological regression/stability (PRECISE 2 - 3) or radiological progression (PRECISE 4 - 5) (B, D). Reprinted with permission from [10].*

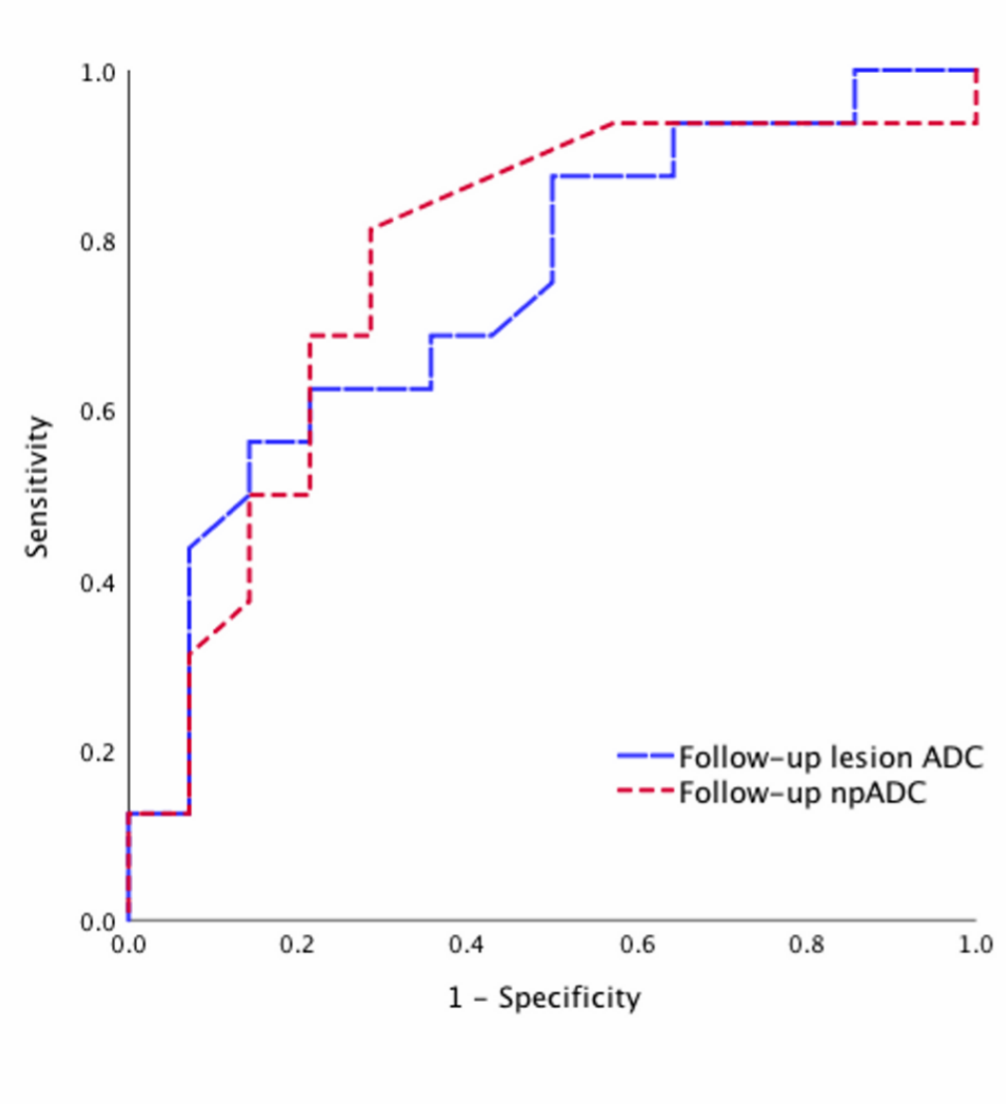



C
1.00
.80
.60
.40
Follow-up npADC ratio
2
3
4
5
PRECISE score


D
1.00
.80
.60
.40
Follow-up npADC ratio
2 - 3
4 - 5
PRECISE score

According to ROC curves analysis (Fig. 24), a cut-off of 0.77 × 10^{-3} mm^2/s for lesion ADC (AUC: 0.74; sensitivity: 68% and specificity: 64%) and a cut-off of 0.59 for npADC ratio (AUC: 0.77; sensitivity: 81% and specificity: 71%) could differentiate between PRECISE 2 - 3 and PRECISE 4 - 5.

Figure 24 *- ROC curves for the detection of radiological progression on the basis of lesion ADC (blue, long-dashed line) and normalised prostatic ADC (npADC) (red, short-dashed line) values at follow-up magnetic resonance imaging. Reprinted with permission from [10].*



6.4 Discussion

My work in collaboration with Professor Panebianco at Sapienza University in Rome has shown that there is substantial agreement between two experienced prostate radiologists using the PRECISE criteria, especially when the PRECISE scores are grouped according to the absence or presence of radiological progression (i.e., PRECISE 1 - 3 vs PRECISE 4 - 5), and I have also observed that the ADC correlates with radiological progression by means of PRECISE score.

In detail, the results presented in this chapter show the first evaluation of the inter-reader variability of the PRECISE score and the first assessment of the inter-reader reproducibility of different ADC calculations and their relationship to the PRECISE score at two different academic centres with high expertise in prostate mpMRI.

From a clinical perspective, the recommendation based on mpMRI to biopsy patients with a PRECISE score ≥ 4 was consistent across me and Professor Panebianco, with $\kappa = 0.83$ and a percent agreement of 90%.

The level of reproducibility of the PRECISE scoring system found in this study relates favourably with that described for other scoring systems. For example, Rosenkrantz et al. reported a substantial agreement for PI-RADS v.2 ($\kappa = 0.59$ in the peripheral zone and $\kappa = 0.51$ in the transition zone for lesions scoring PI-RADS ≥ 4) [5].

It should be pointed out that the PRECISE recommendations are not a rigid scoring system (i.e., there are no systematic flowcharts that can assist inexperienced

readers in scoring the scan), and this is an important difference from the PI-RADS guidelines.

This is a significant aspect of this study, as the pre-existing expertise in prostate MRI of Professor Panebianco and me has been essential to determine the maximal reproducibility in this pilot study.

This is reflected by the high κ coefficients and strong percent agreements to discriminate patients experiencing radiological progression, which means identifying lesions showing suspicious features on mpMRI that should be targeted at biopsy. Therefore, radiological progression should be considered one of the drivers for triggering biopsies together with other clinical and laboratory findings.

It is interesting to observe that the inter-reader agreement was higher for the scans performed at UCLH (κ = 0.81 vs 0.55 per-patient; κ = 0.70 vs 0.48 per-scan), but this was less evident in terms of percent agreement (80% vs 78% and 86% vs 75%, respectively).

A possible reason is that 65% of the persistent negative scans (i.e. PRECISE 3) were from UCLH and only 35% from Sapienza although the inclusion criteria in both centres are similar (i.e. low- or intermediate-risk prostate cancer on AS; ≤ Gleason 3+4 and PSA ≤ 20 ng/ml) and we know that the likelihood of inter-reader agreement is higher for negative MR scans. [6] Also, the differences in PSA density between the two centres seems to be correlated to the risk of progression, as shown by the different patients who received treatment at the two institutions.

The other interesting finding from this multi-centre collaboration is that the absolute ADC value of the lesion and the ADC ratio (normalised to non-cancerous

prostatic tissue) on follow-up imaging are significantly different according to the PRECISE recommendations (i.e., PRECISE 2 - 3 vs PRECISE 4 - 5).

Different studies have shown that ADC values are inversely correlated with the Gleason score (i.e., with the aggressiveness of prostate cancer). [7,8]

However, one of the biggest limitations in DWI is the inter-observer variability when placing the ROI on the ADC map, and reader experience is essential at this regard, especially in the AS setting when DWI is used as a parameter to assess radiological progression. There are no clear recommendations on how (e.g., drawing a single region of interest or by planimetry) and which (absolute *vs* normalised) ADC values should be calculated. It is known that absolute ADC values vary among different MR systems and vendors, and that they are dependent on the number of *b* values acquired. In addition to this, there is also considerable inter- and intra-patient variability.

In my project, I found that both Professor Panebianco and I had a very good agreement in calculating the ADC values at baseline and follow-up imaging.

One of the reasons is certainly that we minimised the aforementioned drawbacks by including only those patients who had been examined on the same MR machine (that means same magnet strength and same DWI protocol) at both time points. We also normalised tumour ADC to that of normal prostatic tissue and urine in the bladder in order to overcome the variability in absolute ADC values.

A significant difference between tumour ADC and normalised pathological ADC ratio at follow-up imaging in terms of radiological progression was observed, but no significant results were seen at baseline imaging. This means that at present baseline ADC cannot predict the likelihood of radiological progression (and further research is needed in this regard) but the results from follow up imaging are

promising. In more detail, we have established two optimal cut-offs to discriminate between PRECISE 2 - 3 and PRECISE 4 - 5 (i.e., lesion ADC: 0.77 × 10^{-3} mm^2/s and npADC ratio of 0.59) and these findings suggest that the ADC at follow up imaging could assist in the identification of patients with radiological progression (who should be biopsied or offered active treatment) and of those without radiological progression (who could initially benefit from clinical and mpMRI follow up).

Again, these results are strengthened by the fact that we minimised the variability related to magnet strengths, vendors and protocols and focused our analysis on patients who had been scanned using always the same machine and the same protocol.

6.4.1 Limitations

A limitation of this pilot study carried out in collaboration with Sapienza University in Rome is that only Professor Panebianco and I assessed the PRECISE score and placed the regions of interest for the ADC values, and therefore we cannot comment on the inter-reader variability of the PRECISE scores for radiologists with different levels of expertise. I acknowledge that the PRECISE scoring system will need to be validated on a larger scale.

Second, as this was a retrospective analysis of patients entering AS for clinical suspicion of prostate cancer, the entry biopsy in both centres was often TRUS-guided, without a clear definition of the lesion location and, as pointed out in the previous chapter, not all patients underwent rebiopsy during follow-up, with targeted resampling often triggered by radiological progression on mpMRI in both centres.

Lastly, it should be acknowledged that an increase in tumour conspicuity (that is one of the main drivers for assessing radiological progression) and the ADC are closely associated, as DWI is the dominant sequence that is used for the assessment of tumours in the peripheral zone.

6.4.2 Conclusions

The results presented in this study suggest that:

- There is substantial reproducibility of the PRECISE score between two experienced radiologists from two different academic centres [9]

- Concordance between readers is highest in discriminating radiological regression/stability (i.e., PRECISE 1 - 3) vs radiological progression (i.e., PRECISE 4 - 5) [9]

- The ADC and the npADC ratio at follow up imaging correlate with radiological progression by means of PRECISE score [10]

- The ADC and the npADC ratio should be recorded in MRI-based AS cohorts along with the PRECISE score. [10]

6.5 Related publications

1. Giganti F, Pecoraro M, Stavrinides V et al. Interobserver reproducibility of the PRECISE scoring system for prostate MRI on active surveillance: results from a two-centre pilot study. Eur Radiol (2020); 30(4):2082–2090.

2. Giganti F, Pecoraro M, Fierro D et al. DWI and PRECISE criteria in men on active surveillance for prostate cancer: a multicentre preliminary experience of different ADC calculations. Magn Reson Imaging (2020); 67:50–58.

6.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study design (publication 1 and 2)
- Acquisition of data: (publication 1 and 2)
- Statistical analysis: (publication 1 and 2)
- Interpretation of data and writing (publication 1 and 2)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1 and 2)
- Professor Valeria Panebianco (publication n. 1 and 2)
- Dr Martina Pecoraro (publication n. 1 and 2)

6.7 References

[1] Giganti F, Moore CM, Robertson NL, et al. MRI findings in men on active surveillance for prostate cancer: does dutasteride make MRI visible lesions less conspicuous? Results from a placebo-controlled, randomised clinical trial. Eur Radiol (2017); 27:4767-4774.

[2] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol (2016); 69:16-40.

[3] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol (2019); 0232:1-12.

[4] Rosenkrantz AB, Kopec M, Kong X, et al. Prostate cancer vs. post-biopsy hemorrhage: diagnosis with T2- and diffusion-weighted imaging. J Magn Reson Imaging (2010);31(6):1387–94.

[5] Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. Radiology (2016); 280(3):793-804.

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[7] De Cobelli F, Ravelli S, Esposito A, et al. Apparent diffusion coefficient value and ratio as noninvasive potential biomarkers to predict prostate cancer grading: comparison with prostate biopsy and radical prostatectomy specimen. Am J Roentgenol (2015); 204:550-557.

[8] van As NJ, de Souza NM, Riches SF, et al. A Study of Diffusion-Weighted

Magnetic Resonance Imaging in men with untreated localised prostate cancer on active surveillance. Eur Urol (2009); 56:981-988.

[9] Giganti F, Pecoraro M, Stavrinides V et al. Interobserver reproducibility of the PRECISE scoring system for prostate MRI on active surveillance: results from a two-centre pilot study. Eur Radiol (2020); 30(4):2082–2090.

[10] Giganti F, Pecoraro M, Fierro D et al. DWI and PRECISE criteria in men on active surveillance for prostate cancer: a multicentre preliminary experience of different ADC calculations. Magn Reson Imaging (2020); 67:50–58.

Chapter 7 The importance of prostate MRI quality: the PI-QUAL scoring system

In this chapter I present the results from a retrospective analysis of the quality of prostate MRI in the PRECISION trial.

The findings presented in this chapter have been published in *European Urology Oncology* [5] and in *The British Journal of Radiology* [8].

7.1 Introduction

The PI-RADS guidelines [1] set out the minimal technical requirements for the acquisition of mpMRI of the prostate. However, the rapid diffusion of this technique has inevitably led to variability in scan quality among centres across the UK and the world. High-quality MR images of the prostate are a key determinant in an MRI-led prostate cancer diagnostic pathway. MRI-derived targeted biopsies are used to detect clinically significant prostate cancer and a negative scan of adequate quality can be used to safely avoid unnecessary immediate biopsy.

It is known that suboptimal image acquisition diminishes the sensitivity and specificity of this technique for the detection of clinically significant prostate cancer, as this may result in less men with clinically significant disease being biopsied (underestimation) or in more men with indolent disease receiving treatment rather than a conservative approach such as AS (overcalling). In turn, this could result in clinicians and patients losing confidence in the technique.

For either detection or exclusion of clinically significant prostate cancer, images with good spatial resolution and high signal-to-noise ratio for each MR sequence (T2-WI, DWI and DCE) are needed, and new tools to help centres to improve the quality of their prostate MR scans would be really useful.

Therefore, there is growing evidence that a formal assessment of prostate MRI quality is needed.

A UK consensus meeting [2] has stressed the importance of ensuring high-quality MR acquisition and reporting, especially if prostate mpMRI is used as a means of avoiding biopsy, as shown in the PRECISION trial. [3]

In addition to this, a recent consensus paper from the European Society of Urogenital Radiology (ESUR) and the EAU Section of Urologic Imaging (ESUI) has shown that there is still huge variability in the conduct of prostate mpMRI and has highlighted the need to define requirements for learning and accumulation of reporting experience for mpMRI, but a set of objective criteria for assessing image quality has not been provided. [4]

This is why one of the objectives of my PhD has been to fill this gap.

The importance of prostate mpMRI quality is in fact crucial also in the AS setting, where serial MR scans are acquired over time and the imaging quality needs to be adequate in order to compare the different studies in a proper and reliable manner.

The multicentre, randomised PRECISION trial showed the superiority of mpMRI-targeted biopsy over standard TRUS-guided biopsy in 500 biopsy-naïve men. [3] During the quality assurance work in PRECISION, computer-generated random sequences were used to select 25% of each centre's scans (number of centres = 22) at random. All centres wishing to participate in PRECISION were initially asked to provide an audit of their biopsy-based outcomes of over 100 patients together with a selection of MR scans. Some centres were given focussed suggestions to improve their scan quality in order to be able to join the study.

As part of this PhD, I retrospectively reviewed a selection of scans from men included in PRECISION, across 22 different centres, along with a senior consultant radiologist (Dr Clare Allen) at our hospital using objective criteria in line with the PI-RADS v. 2 guidelines [6], as PI-RADS v2.1 guidelines [7] had not been published at the time of the trial.

We introduced additional objective criteria to specifically address the quality of each reviewed scan, which we reported together after discussion.

We then created a dedicated scoring system that we have continued to develop in our London Cancer network as part of an ongoing quality improvement project, and that will be now shown and discussed. [5]

7.2 Methods

The multicentre, randomised PRECISION trial showed the superiority of mpMRI-targeted biopsy over standard TRUS-guided biopsy in 500 biopsy-naïve men [clinically significant cancer: 38% and 26% (p = 0.005) and clinically insignificant cancer: 9% and 22% (p < 0.001) in the MR-targeted and standard-biopsy group, respectively]. [3] During the quality assurance work in PRECISION, computer-generated random sequences were used to select 25% of each centre's scans at random that we used to develop a scoring system called the Prostate Imaging Quality (PI-QUAL) score (Table 45), which includes a scale from 1 to 5 to evaluate the quality of each scan.

Table 45 *- Assessment of the diagnostic quality of multiparametric MRI scans using the PI-QUAL score. Reprinted with permission from [5].*

PI-QUAL score	Criteria	Clinical Implications
1	All mpMRI sequences are below the minimum standard for diagnostic quality	It is NOT possible to rule in all significant lesions * It is NOT possible to rule out all significant lesions *
2	Only one mpMRI sequence is of acceptable diagnostic quality	
3	At least two mpMRI sequences taken together are of diagnostic quality	It is possible to rule in all significant lesions It is NOT possible to rule out all significant lesions
4	Two or more mpMRI sequences are independently of diagnostic quality	It is possible to rule in all significant lesions It is possible to rule out all significant lesions
5	All mpMRI sequences are of optimal diagnostic quality	

Legend: PI-QUAL: Prostate Imaging QUALity; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System

* Therefore, reports should not include PI-RADS or Likert scores

Each sequence was given a summary binary outcome for whether or not the sequence was of diagnostic quality and an overall final PI-QUAL score was given. For this purpose, we used a dedicated scoring sheet that is shown in Fig. 25 (next page).

7.3 Results

Overall, the mpMRI quality in the centres participating in PRECISION was good.

MpMRI quality was of at least sufficient diagnostic quality (PI-QUAL ≥ 3) for 55 scans (95%) and good or excellent (PI-QUAL ≥ 4) for 35 scans (60%). Twelve scans (21%) had a score of 5, 23 (40%) had a score of 4, 20 scans (34%) had a score of 3, and three scans had a score < 3. Fifty-five out of 58 (95%) scans were of diagnostic quality for T2-WI, followed by DWI (46/58 scans; 79%), and DCE (38/58 scans; 66%).

There was very good adherence to PI-QUAL quality criteria for T2-WI.
The position of the axial plane varied between institutions (e.g., perpendicular to the MR table, orthogonal to the rectum or in an oblique axial plane matching the long axis of the prostate) but the other sequences (DWI and DCE) were all acquired in the same plane. Only three scans had a PI-QUAL score < 3, due to inadequate in-plane and spatial resolution (n = 1) or severe motion artefacts (n = 2).

Fig. 25 *- Scoring sheet for assessing the quality of multiparametric magnetic resonance imaging using the PI-QUAL scoring system. T2-WI = T2-weighted imaging; DWI = diffusion-weighted imaging; DCE = dynamic contrast–enhanced; ADC = apparent diffusion coefficient.*

Reprinted with permission from [5].

Scan & site number:

PRECISION

Prostate Imaging QUALity control (PI-QUAL) scoring sheet

PI-QUAL score	Criteria	Clinical implications
1	All mpMRI sequences are below the minimum standard of diagnostic quality	It is NOT possible to rule in all significant lesions § It is NOT possible to rule out all significant lesions §
2	Only one mpMRI sequence is of acceptable diagnostic quality	
3	At least two mpMRI sequences taken together are of diagnostic quality	It is possible to rule in all significant lesions It is NOT possible to rule out all significant lesions
4	Two or more mpMRI sequences are independently of diagnostic quality	It is possible to rule in all significant lesions It is possible to rule out all significant lesions
5	All mpMRI sequences are of optimal diagnostic quality	

§ Therefore reports should not include PI-RADS or Likert scores

Please (✓) if present: (note: '*adequate*' means compliant with the technical specifications reported in PI-RADS v. 2 guidelines) *

T2-WI		DWI		DCE	
Technical parameters		**Technical parameters**		**Technical parameters**	
Axial plane		Axial plane matching T2-WI		Axial plane matching T2-WI	
Sagittal or coronal plane		Adequate field of view		Adequate field of view	
Adequate field of view		Adequate in-plane resolution		Adequate in-plane resolution	
Adequate in-plane resolution		Adequate slice thickness		Adequate slice thickness	
Adequate slice thickness		Multiple [> 2] *b* values acquired		Pre-contrast T1-WI available	
Z-axis correctly positioned		High *b* value (synthesised or acquired)		Fat suppression/subtraction	
Visual assessment		**Visual assessment**		Adequate temporal resolution [≤ 10 sec]	
Capsule clearly delineated		Adequate ADC map		Adequate total observation rate [≥ 2min]	
Seminal vesicles clearly delineated		Absence of artefacts (e.g. rectal air)		**Visual assessment**	
Ejaculatory ducts clearly delineated				Capsular vessels clearly delineated	
Neurovascular bundles clearly delineated				Vessels in the Alcock's canal clearly delineated	
Sphincter muscle clearly delineated				Absence of artefacts (e.g. movement)	
Absence of artefacts (e.g. movement)					

Is T2-WI of diagnostic quality? ☐ Yes ☐ No

Is DWI of diagnostic quality? ☐ Yes ☐ No

Is DCE of diagnostic quality? ☐ Yes ☐ No

PI-QUAL score: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Comments:

Date:

Reporting Radiologist:

Signed:

* Weinreb JC, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40.

For DWI, 34/58 scans (59%) were lacking a dedicated single high *b* value acquisition, even though PI-RADS v. 2 guidelines recommend at least a minimum *b* value of 1,400 s/mm^2 at 1.5T (but up to 2,000 s/mm^2, if adequate signal-to-noise ratio permits). We also observed that 7/58 scans (12%) had synthesised (i.e., computer-generated *b* values) rather than acquired ADC map, and DWI was not of diagnostic quality for these scans.

The highest variability in quality of mpMRI sequences was for DCE.
A temporal resolution of < 10 seconds (preferably < 7 seconds) is recommended by PI-RADS v. 2 guidelines but only 31/58 scans (53%) matched the cut-off of 10 seconds. However, we know from PI-RADS v 2.1 guidelines (which were published after the PRECISION study) that temporal resolution can be increased to 15 seconds in order to achieve higher spatial resolution, and 21/23 centres (91%) participating in the PRECISION trial had a temporal resolution of ≤ 15 seconds. We also know that fat suppression is very important to optimise the contrast-to-noise ratio, but 26/58 scans (45%) in this study did not have subtracted or fat-suppressed DCE images.

Figg. 26, 27 and 28 (next pages) show a combination of poor and good quality images for each MR sequence.

Fig. 26 *- Axial T2-WI images showing a suboptimal (A) and a good (B) quality MR scan.*

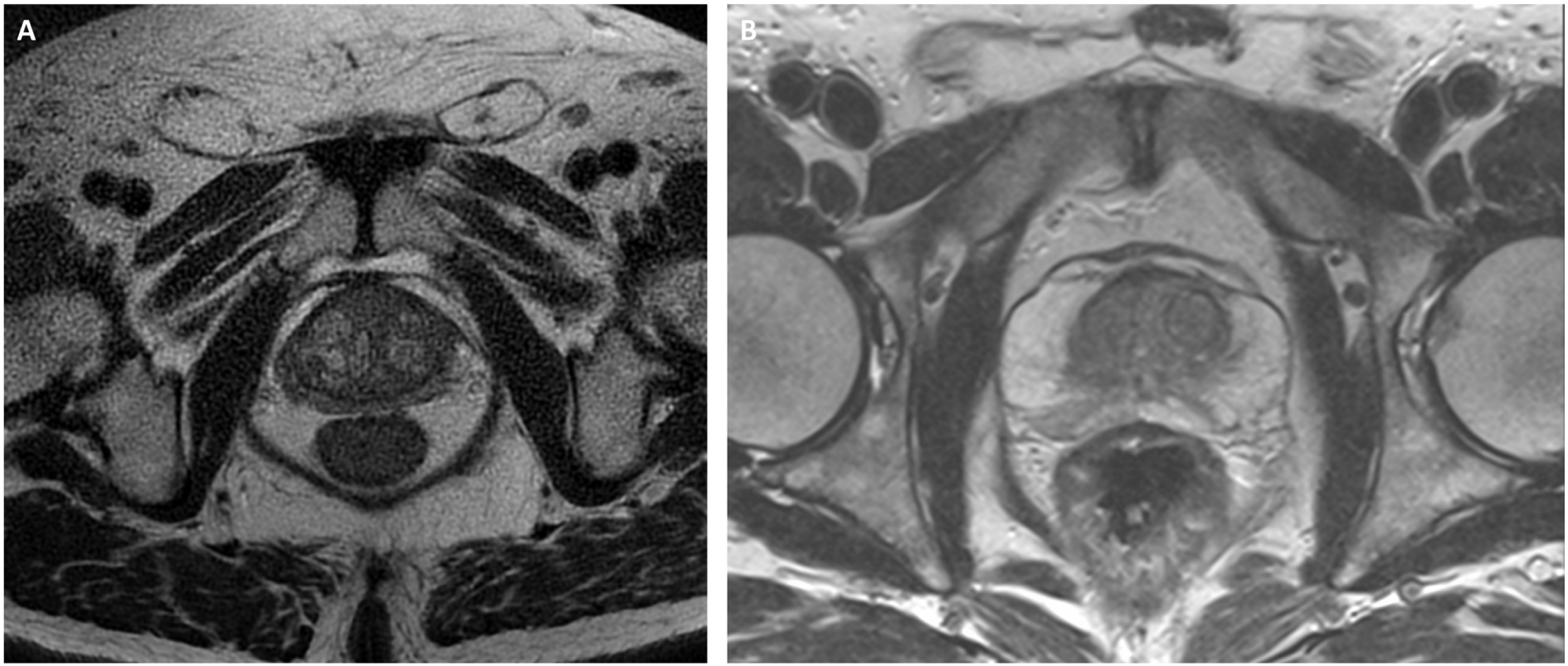


Fig. 27 *- DWI of a suboptimal long b sequence (A) and ADC map (B), and of a long b sequence (C) and ADC map (D) of a good quality scan.*

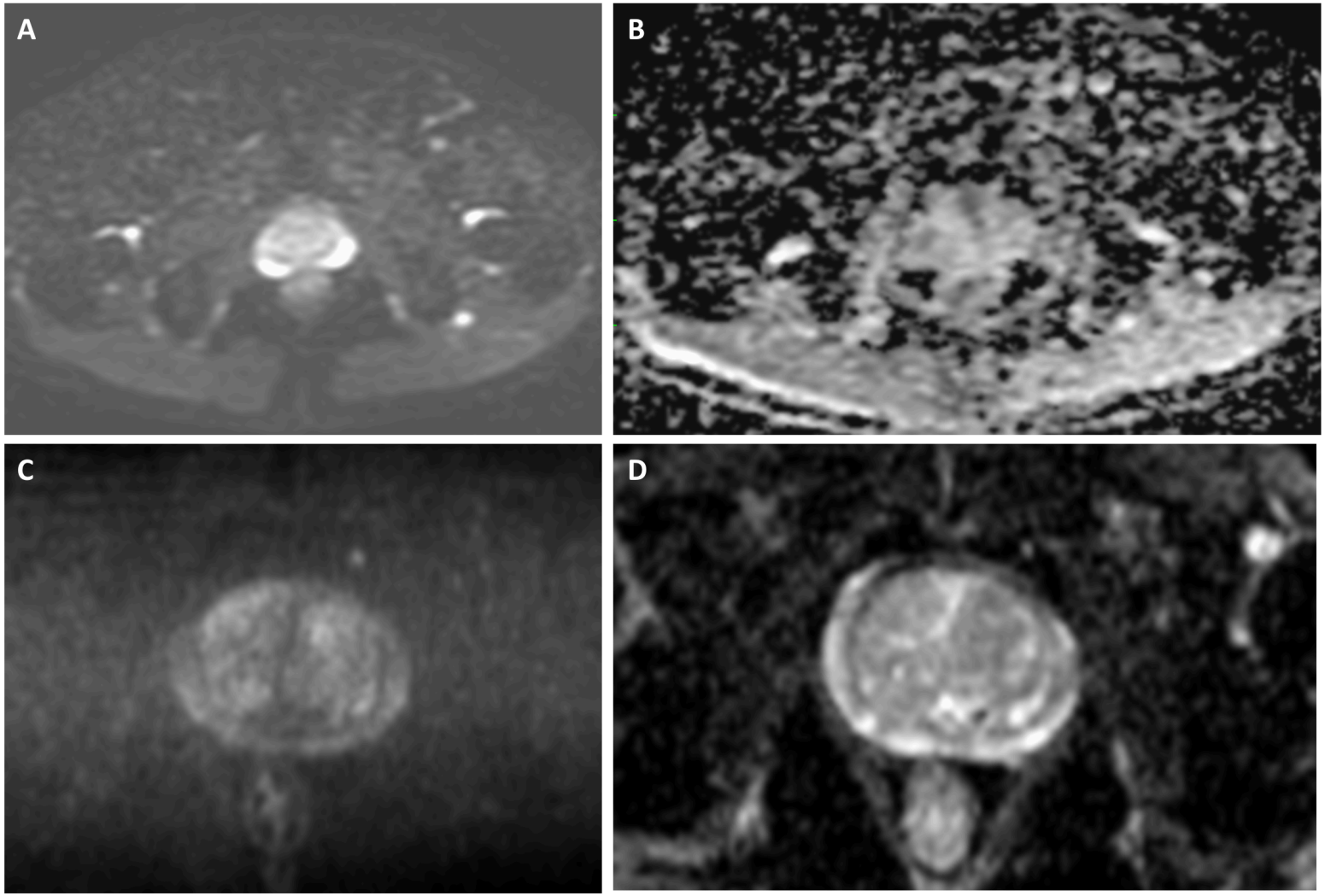
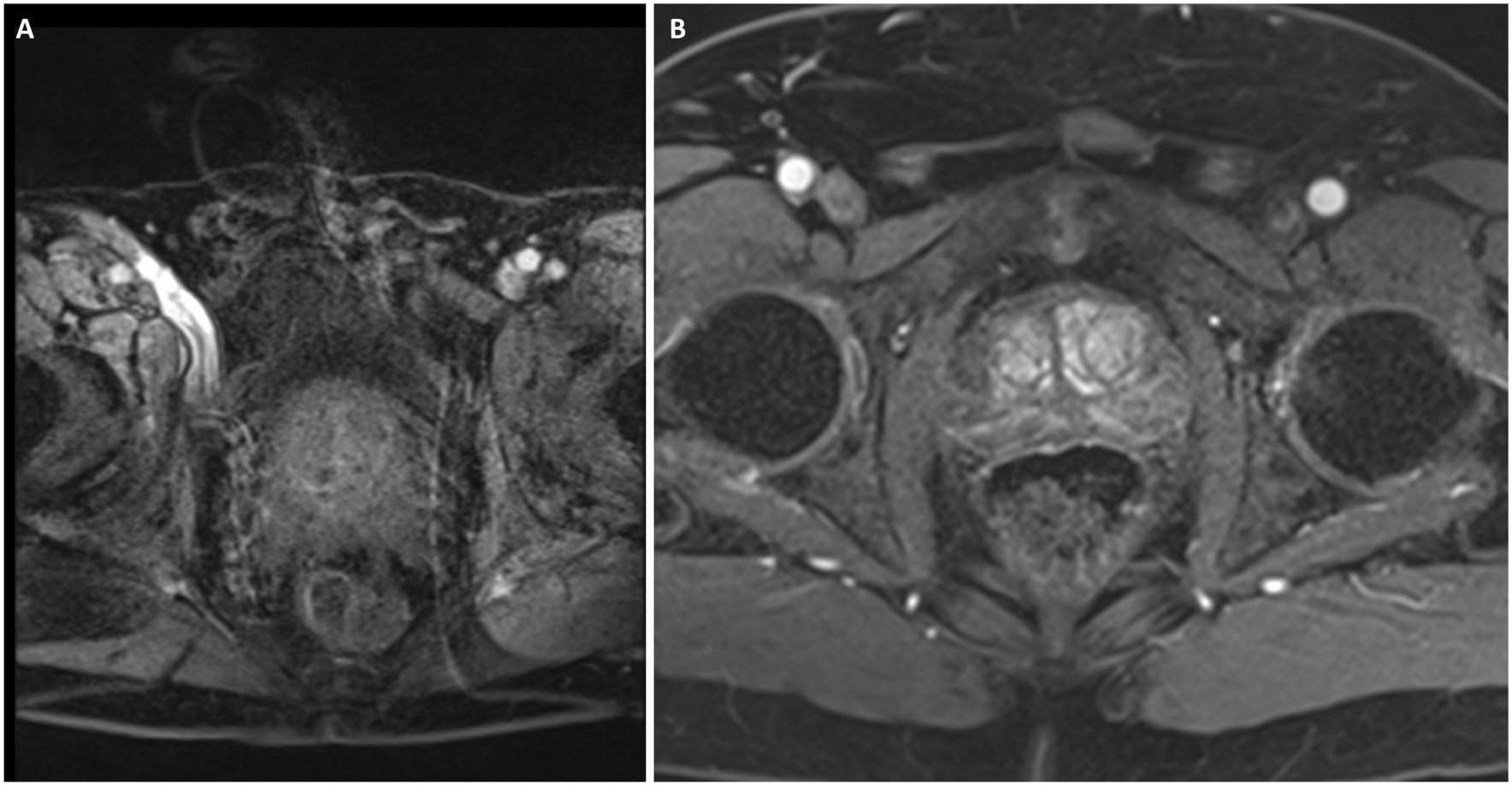


Fig. 28 *- DCE images of a suboptimal (A) and a good (B) quality MR scan.*



7.4 Discussion

The PI-QUAL score is based on a 1-to-5 scale derived by evaluating each mpMRI sequence against a defined set of objective quality criteria in line with PI-RADS v.2 guidelines and using a subjective assessment of the image.

There can be significant variability in the acquisition of prostate mpMRI and often adherence to the PI-RADS guidelines does not necessarily lead to a diagnostic quality image. For example, although it is well known that the ADC correlates inversely with adverse histology in prostate cancer, there is still considerable overlap between benign prostatic hyperplasia, low-grade and high-grade tumours.
Although the PI-RADS v. 2.1 guidelines suggest a threshold of 750-900 μm^2/sec to differentiate between benign and malignant prostate tissue, ADC calculations are influenced by the choice of *b* values and cannot be standardised due to the inconsistency across vendors (even though the ADC standardisation of prostate cancer can be obtained, for example, on a single scanner with respect to the normal prostatic tissue or to the urine in the bladder). Thus, visual assessment is often used as the primary method to assess the quality of DWI.
In addition to this, other factors related to the patient (e.g., patient motion, patient size, or the degree of rectal distension) or dependent on the expertise of the radiographer acquiring the MR study, could heavily impact on the quality of prostate mpMRI.

It follows that a poor-quality scan should not be used for a diagnostic assessment of the prostate.

During the quality assurance work from PRECISION, I noted that the highest variability in quality was for DCE sequences, followed by DWI and T2-WI. This may explain why some centres have been able to drop the DCE sequence with no effect on their ability to diagnose significant prostate cancer. Scanner age is also a significant factor that influences the quality of prostate mpMRI.

This requires more investigation but from our experience at UCLH, MR scanners over 10 years old are not able to produce diagnostic quality studies.
In addition to this, the results from an audit by Burn and colleagues showed a significant difference in prostate MR quality at a 7-year cut-off for scanner age. [8] In that study, the influence of scanner age on image quality was assessed by comparing two groups: MRI performed on scanners < 7 years old (54 patients) and MRIs performed on scanners ≥ 7 years old (40 patients) and dichotomising image quality according to a dedicated 1-to-5 scoring system into diagnostic (score ≥ 3) and non-diagnostic (score < 2) scans. The results were significant for T2-WI, where 80% examinations were diagnostic in the newer scanner group, compared to 53% in the older scanner group (odds ratio 3.5, p= 0.006). The Authors concluded that scanner age was a significant factor influencing T2-WI image quality. They used a cut-off of 7 years for defining “older” scanners, as this was in line with their UK regional guidelines.

In addition to this, the European Coordination Committee of the Radiological, Electromedical and Healthcare IT industry (COCIR) ‘Golden Rules’ [9] state that:

1. At least 60% of the installed equipment base should be less than five years old.

2. No more than 30% of the installed equipment base should be between six to ten years old.
3. No more than 10% of the age profile should be more than ten years old.

Although further investigation is needed, it is fair to highlight that lack of investment in new scanners may prove a major obstacle to improving the quality of prostate MRI.

We can confirm that the adherence to the minimum acceptable technical parameters of mpMRI as per PI-RADS v. 2.1 guidelines is a good starting point to improve the quality of prostate MR. However, this is just a guide and the quality can also be improved using newer fat saturation techniques, parallel imaging and motion reduction techniques. Often the sequences that are preloaded by the MR vendor are not of sufficient quality for prostate imaging and it is important to work with the radiographers and physicists until a diagnostic set of sequences is obtained in each centre.

Further research on what is most important in these technical guidelines and perhaps the formation of a sequence bank for sharing best practice to improve mpMRI quality along with the use of automated methods (including those based on deep learning) is advocated. For example, a solution might be that centres using the same scanner could share their MR protocols by downloading a scan and then send it to the new scanner to improve the consistence across centres.
In addition to this, broad consensus among experts should be reached before using PI-QUAL in clinical settings, as some image features will need to be refined, such as

which axial plane acquisition should be defined as “optimal” and how should the quality of the dominant sequence be weighted in the final assessment of the score. Finally, it is necessary to clarify whether synthesised and acquired high *b*-value acquisitions should be weighted equally and if the quality of the ADC map is linked to this.

I am currently co-leading with Dr. Maarten De Rooij (a genitourinary radiologist based in Nijmegen, The Netherlands) a project on prostate MR quality in collaboration with the ESUR / ESUI prostate MR working group and two other international experts in the field (Professor Masoom Haider from Canada and Dr. Baris Turkbey from the United States).

We are currently discussing how we can further refine PI-QUAL (e.g., reducing to only 10 criteria to assess MR quality: four items for T2-WI, four for DWI and two for DCE) and we aim to test the new version on a dedicated set of scans from different scanners, vendors and centres in the next 6 months.

In conclusion, the first version of PI-QUAL [5] represents the start of identifying a framework for the assessment of prostate MR quality and will give clinicians confidence to act on the scan findings and help to reduce scan variability but further refinements and prospective validation are envisaged.

7.5 Related publications

- Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V, PRECISION study group. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. Eur Urol Oncol (2020); 3(5):615-619.

- Giganti F, Allen CA. Imaging quality and prostate MR: it's time to improve. Br J Radiol (2020) in press. doi: 10.1259/bjr.20200934

7.6 Statement of contribution

My personal contribution to the works published in this chapter is as follows:

- Study concept (publication n. 1 and 2)
- Study design (publication n. 1 and 2)
- Acquisition of data (publication n. 1 and 2)
- Statistical analysis (publication n. 1)
- Interpretation of data and writing (publication n. 1 and 2)

Other key contributors to the works presented in this chapter:

- Professor Caroline M Moore (publication n. 1)
- Dr Clare Allen (publication n. 1 and 2)
- Dr Veeru Kasivisvanathan (publication n. 1)

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1. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol (2019);0232:1–12.
2. Brizmohun Appayya M, Adshead J, Ahmed HU, et al. National implementation of multiparametric magnetic resonance imaging for prostate cancer detection: recommendations from a UK consensus meeting. BJU Int (2018); 122:13–25.
3. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate Cancer Diagnosis. N Engl J Med (2018);378:1767–77.
4. De Rooij M, Israel B, Tummers M, et al. ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. Eur Radiol (2020); 30(10):5404-5416.
5. Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V, PRECISION study group. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. Eur Urol Oncol (2020); 3(5):615-619.
6. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, version 2. Eur Urol (2016); 69:16-40.
7. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol (2019);0232:1–12.
8. Burn PR, Freeman SJ, Andreou A, Burns- Cox N, Persad R, Barrett T. A multicentre assessment of prostate MRI quality and compliance with UK and international standards. Clin Radiol 2019; 74: 894.e19–894.e25.

9. European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry (COCIR). Medical imaging equipment age profile and density. Brussels: COCIR, 2016.

Chapter 8 Future directions and conclusions

The work presented in my thesis has confirmed the promising role of mpMRI in the AS setting and suggests that the PRECISE score has all the attributes to become a tool to measure disease progression.

In order to do this, it is imperative that the MR scan is of good diagnostic quality, and I have shown that quality can be measured by using a dedicated scoring system (PI-QUAL).

8.1 Summary of key findings from this thesis

I have reported in Chapter 2 that there has been increasing interest in the use of mpMRI during AS over the last decade, and this technique has now become commonplace in AS candidates' selection in the UK, due to its high negative predictive value for clinically significant prostate cancer. In Chapter 3 I reported data analysis from the MAPPED study in men on AS, showing that Dutasteride does not affect tumour conspicuity on T2-WI but does so on DWI.

In Chapter 4 I reported my work with an expert international panel to establish a new reporting standard (PRECISE score) for mpMRI during AS. I outlined the PRECISE recommendations and case report form that can be used to report serial mpMRI scans in men on AS, to document radiological change over time and I have discussed the first software (MIM® PRECISE reporting tool) that I have created with industry, demonstrating quicker reporting of the PRECISE recommendations. In Chapter 5 I reported the application of the PRECISE score in our UK cohort at UCLH

and I found that the PRECISE score can identify patients on AS who are progressing radiologically (i.e., PRECISE 4 - 5) in a timely manner, promoting re-biopsy/treatment, and I showed that the ellipsoid formula for calculating tumour volume on MRI is strongly correlated with planimetry and could be used to monitor tumour volume on mpMRI during AS.

In Chapter 6 I reported the results from my 2-month Bracco fellowship (European School of Radiology, 2019) and the UCL Erasmus+ programme, thanks to which I observed a substantial reproducibility of the PRECISE score between myself and Professor Panebianco from Sapienza University in Rome. In Chapter 7 I presented a dedicated scoring system (PI-QUAL) from the PRECISION trial that represents the start of identifying a framework for the assessment of prostate MR quality and I concluded that PI-QUAL can give clinicians confidence to act on the scan findings and help to reduce scan variability, but I have also acknowledged that PI-QUAL represents only the first step and will definitely require further refinement and prospective validation in future work.

8.2 Achievements and challenges during my PhD

My thesis describes the role that MRI is gaining in patients on AS and the importance of good quality MRI, especially during AS. I am confident that my work is promoting the shift of this technique from being only a diagnostic technique to one that can be applied in patients on AS, as also supported by the UK NICE guidelines, but there are still challenges ahead.

For example, one of the biggest challenges that I encountered during my PhD has been the acceptance from the international community that mpMRI may offer an opportunity to follow patients on AS without the need of performing further biopsies in the absence of signs of radiological progression. Although I have always acknowledged that robust data from prospective studies are still needed before widespread adoption of mpMRI as a tool to replace repeat biopsies during AS, some reviewers have pointed out that the lack of confirmatory biopsy and the different intervals between our MR scans at UCLH (that reflect our two different AS pathways according to the presence or absence of a visible lesion at baseline MRI) represented a major limitation of the work presented in this thesis. On the contrary, I believe that our results represent a real-world scenario in which biopsies are recommended at the discretion of the treating physician (based either on radiological progression or adverse PSA kinetics) and also where some men, particularly those with Gleason 3+4 disease at the outset of AS, might not wish to have a further biopsy before proceeding to treatment. This represents one of the challenges ahead, and I will make sure that a further iteration of PRECISE will address this.

Another challenge has been the initial collaboration with the ESUR / ESUI prostate MR working group with regards to the PI-QUAL score, as the members of the prostate MR working group would prefer downplaying the importance of DCE with respect to T2-WI and DWI (due to the growing uptake of biparametric MRI by many centres), while PI-QUAL gives each sequence the same weighting.
However, this is still a matter of debate (as at present there are no robust trials that show a similar accuracy in the detection of clinically significant prostate cancer between mpMRI and biparametric MR) and we are currently discussing how we can

further refine PI-QUAL (e.g., reducing to only 10 criteria to assess MR quality: four items for T2-WI, four for DWI and two for DCE).

There is also discussion over whether a simple 5-point score is more user-friendly and thus be more likely to be used than a more complex score for prostate MRI quality. It has been suggested that with diagnostic scores (PI-RADS and Likert) having a 1-5 score already, an A t o E rating might be easier to integrate into the clinical lexicon for prostate MRI reporting.

The biggest challenge ahead in terms of prostate MRI quality is the use of high-quality scans on a wider scale, especially in the AS setting, as there are still many centres across the world whose prostate MRI is of suboptimal diagnostic quality. There are different reasons for variation in prostate MRI quality, including scanner age (i.e., from our preliminary work and our experience at UCLH, MR scanners over 10 years old are not able to produce diagnostic quality studies), technical parameters related to image acquisition and patient-related factors (e.g., artefacts due to movement or the presence of metal implants).

8.3 Future directions

In order to overcome the challenges ahead, I have just been awarded a competitive Prostate Cancer Foundation (PCF) Young Investigator Award for the next three years (2021-2024). Thanks to this funding and to a philanthropic donation from the same donor who funded this PhD, I will be able to:

1. Continue the prospective reporting of our cohort at UCLH and analyse different established cohorts of men on AS from our international academic collaborators in order to create a risk calculator to define what constitutes ‘radiological progression’ in men at highest risk of developing aggressive disease (i.e., PRECISE 4 and 5)

2. Organise a new PRECISE consensus meeting, where the results will be discussed, and the PRECISE v. 2.0 recommendations will be drafted and published

3. Work on the refinement of PI-QUAL and promote its application on a wider scale.

8.4 Conclusion

In conclusion, in my thesis I have demonstrated that mpMRI is a valuable technique in patients on AS, as also shown by the interest of other international groups in the application of the PRECISE score in their own cohorts, and that PI-QUAL is a promising scoring system for an objective assessment of prostate MRI quality.

Although there are still challenges ahead, my view is that these are doable, and I really look forward to seeing the application of the PRECISE score and of PI-QUAL to assess prostate MRI quality on a large and robust scale.

Chapter 9 Appendices

9.1 Full list of my publications related to this PhD (only First / Senior author)

- Giganti F, Moore CM. MRI in early detection of prostate cancer. Curr Opin Urol (2019); 29(6):563-568.
- Giganti F, Rosenkrantz AB, Villeirs G, et al. The Evolution of MRI of the Prostate: The Past, the Present, and the Future. AJR Am J Roentgenol (2019); 213(2):384-396.
- Giganti F, Stavrinides V., Moore C.M. (2018) Can MRI Replace Biopsy in Men on Surveillance? Book chapter in: Klotz L. (eds) Active Surveillance for Localized Prostate Cancer. Current Clinical Urology. Humana Press, Cham.) edited by Laurence Klotz.
- Giganti F, Moore CM. Magnetic resonance imaging in active surveillance - a modern approach. Transl Androl Urol (2018); 7(1):116-131.
- Giganti F, Stabile A, Moore CM. Magnetic resonance imaging and prostate cancer: perspectives from the UK, Europe and USA. Arch Esp Urol (2019); 72(2):135-141.
- Giganti F, Moore CM, Robertson NL, et al. MRI findings in men on active surveillance for prostate cancer: does dutasteride make MRI visible lesions less conspicuous? Results from a placebo-controlled, randomised clinical trial. Eur Radiol (2017); 27(11):4767-4774.
- Giganti F, Gambarota G, Moore CM, et al. Prostate cancer detection using quantitative T2 and T2 -weighted imaging: the effects of 5-alpha-reductase

inhibitors in men on active surveillance. Magn Reson Imaging (2018); 47(6):1646-1653.

- Moore CM *, Giganti F *, Albertsen P, et al. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations - A Report of a European School of Oncology Task Force. Eur Urol (2017); 71:648-655. * *shared first authorship*
- Giganti F, Allen C, Piper JW, et al. Sequential prostate MRI reporting in men on active surveillance: initial experience of a dedicated PRECISE software program. Magn Reson Imaging (2018); 57:34-39.
- Giganti F, Kirkham A, Allen C, et al. Update on multiparametric prostate MRI during active surveillance: current and future trends and role of the PRECISE recommendations. AJR July 29, 2020. Accepted manuscript (in press) doi:10.2214/AJR.20.23985
- Giganti F, Stabile A, Stavrinides V, et al. Natural history of prostate cancer on active surveillance: stratification by MRI using the PRECISE recommendations in a UK cohort. Eur Radiol. (2020) (in press) doi: 10.1007/s00330-020-07256-z.
- Giganti F, Moore CM, Punwani S, Allen C, Emberton M, Kirkham A. The natural history of prostate cancer on MRI: lessons from an active surveillance cohort. Prostate Cancer Prostatic Dis. (2018); 21(4):556-563.
- Giganti F, Stavrinides V, Stabile A, et al. Prostate cancer measurements on serial MRI during active surveillance: it's time to be PRECISE. Br J Radiol. (2020) (in press) doi: 10.1259/bjr.20200819.
- Giganti F, Pecoraro M, Stavrinides V et al. Interobserver reproducibility of the PRECISE scoring system for prostate MRI on active surveillance: results from a two-centre pilot study. Eur Radiol (2020); 30(4):2082–2090.

- Giganti F, Pecoraro M, Fierro D et al. DWI and PRECISE criteria in men on active surveillance for prostate cancer: a multicentre preliminary experience of different ADC calculations. Magn Reson Imaging (2020); 67:50–58.
- Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V, PRECISION study group. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. Eur Urol Oncol (2020); 3(5):615-619.
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- Giganti F, Kasivisvanathan V, Allen C, Moore CMM. The Importance of Being PRECISE in Prostate Magnetic Resonance Imaging and Active Surveillance. Eur Urol (2021) in press. doi: 10.1016/j.eururo.2021.01.016
- Moore CMM, Cole AP, Allen C, Giganti F. Let's follow the Golden Mean: using Magnetic Resonance Imaging to determine the need for biopsy in men on active surveillance. Eur Urol Oncol (2020) in press. doi: 10.1016/j.euo.2020.11.009.

9.2 Related Research presentations

Congress	Location	Date
ECR congress (virtual)	Vienna, Austria	March 2021
RSNA congress (virtual)	Chicago, USA	December 2020
EAU congress (virtual)	Amsterdam, The Netherlands	July 2020
ECR congress (virtual)	Vienna, Austria	July 2020
Prostate MRI masterclass	Rome, Italy	May 2020
EAU Prostate MRI webinar	Amsterdam, The Netherlands	April 2020
RSNA congress	Chicago, USA	December 2019
ESUR prostate MRI course	Rome, Italy	June 2019
ISMRM Italian chapter	Milan, Italy	March 2019
EAU congress	Barcelona, Spain	March 2019
ECR congress	Vienna, Austria	March 2019
Pelican Cancer Foundation	Manchester, UK	February 2019
RSNA congress	Chicago, USA	November 2018
ESUR prostate MRI course	Lille, France	June 2018
ISMRM congress	Paris, France	June 2018
AUA congress	Boston, USA	May 2017
EAU congress	London, UK	March 2017
ECR congress	Vienna, Austria	March 2016

9.3 Grants, awards and prizes

1. UCL Graduate Research Scholarship (2017-2020)

   https://www.ucl.ac.uk/scholarships/graduate-research-scholarships

2. Philanthropic donation by Pierre and Julia Brahms in memory of Chris Adams

3. ESOR Bracco Clinical Fellowship 2019

   https://www.esor.org/training-programmes/bracco-fellowships/

4. Erasmus UCL Talent Staff Mobility Programme (London/Rome)

   https://www.ucl.ac.uk/human-resources/learning-development/career-support-opportunities/erasmus

5. UCL Cities Partnership Programme Award (London/Paris)

   https://www.ucl.ac.uk/global/cities-partnerships-programme/paris

6. Lee Rogers ARRS Editorial fellowship 2021

   https://www.arrs.org/ARRSLIVE/RogersFellowship

7. Prostate Cancer Foundation (PCF) Young Investigator Award 2020

   https://www.pcf.org/c/young-investigator-award-class-of-2020/

8. Best oral presentation at European Congress of Radiology 2015, Vienna, Austria

9. Best poster at European Congress of Urology 2019, Barcelona, Spain

10. Winner of the ISMRM 2018 Clinical Stipend Programme, ISMRM, Paris, France

11. 2020 Top 10 Best Reviewer for *European Urology Oncology*.

12. 2020 Winner of the SoME Award for the most influential paper on *European Urology Oncology:*