



Original contribution

Sequential prostate MRI reporting in men on active surveillance: initial experience of a dedicated PRECISE software program

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ABSTRACT

Background and objectives: There is interest in using sequential multiparametric magnetic resonance imaging (mpMRI) to assess men on active surveillance (AS) for prostate cancer. The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations propose standardised reporting mpMRI data for these men. This includes accurate size measurements of lesions over time, but such approach is time consuming for the radiologist and there is a strong need of dedicated tools to report serial scans in a systematic manner. We present the results from an initial validation cohort using dedicated PRECISE reporting software to allow automated comparison between sequential scans on AS.

Materials and methods: We retrospectively analysed baseline and follow-up scans of 20 men randomised to 6 months of daily dutasteride (n = 10) or placebo (n = 10) from the MAPPED trial. Men underwent 3T mpMRI at baseline and after 6 months, and a dedicated radiologist reported the scans using both a widespread commercially-available platform (Osirix®) and a semi-automated dedicated PRECISE reporting tool (MIM®). Tumour volume by planimetry in all sequences and conspicuity on diffusion-weighted imaging were assessed. Reporting time was recorded, and we used the Wilcoxon test for statistical analysis.

Results: Median tumour volumes and conspicuity were similar using both approaches. The reporting time of the follow-up scan was quicker using the PRECISE reporting workflow both in the whole population (12'33" vs 10'52"; p = 0.005) and in the dutasteride arm (15'50" vs 12'59"; p = 0.01). A structured report including clinical and imaging data was generated according to the PRECISE recommendations and a comparison table between lesion characteristics at baseline and follow-up scans was also included.

Conclusion: We conclude that a dedicated PRECISE reporting tool for sequential scans in men on AS results in a significant reduction in the reporting time and allows the radiologist to easily compare scans over time. This tool will help with our understanding of the natural history of mpMRI changes during AS.

1. Introduction

Men with low and intermediate risk prostate cancer (PCa) are offered active surveillance (AS) to defer or avoid radical treatment and its potential side effects, without missing the opportunity for cure [1,2].

There is evidence that multiparametric magnetic resonance imaging (mpMRI) shows potential in identifying AS candidates, who may have little benefit from therapy but still need to be continuously monitored to allow prompt curative treatment if the disease shows signs of becoming more aggressive [3]. However, the use of mpMRI in men on AS

Abbreviations: PCa, prostate cancer; AS, active surveillance; MpMRI, multiparametric magnetic resonance imaging; PRECISE, Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; ADC, apparent diffusion coefficient; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate specific antigen; T2-WI, T2-weighted imaging; DWI, diffusion-weighted imaging; DCE, dynamic contrast-enhanced; IQR, interquartile ranges

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varies between countries and health systems, with a lower use of mpMRI outside of academic institutions [4].

As a result, many men have more frequent and invasive testing than needed, at a cost to them and the health care system, and a small number of men will eventually have significant disease detected too late, increasing the likelihood of metastatic spread. Additionally, there are few published data to inform us on any specific radiological change to define the progression of the disease (e.g. volume, change in lesion size or appearance over time, quantitative parameters like the apparent diffusion coefficient -ADC-, etc.) that should prompt biopsy or active treatment [5–7].

Morgan et al. [5] reported the results of 151 men on AS undergoing mpMRI at two time points (median interval 1.9 years). They showed that tumour volume increased measurably in 34.4% of men after 2 years of AS, and that change in ADC could be used to identify tumours with measurable growth ($-6.8\% \pm 12.3\%$ for men with measurable growth vs $0.23\% \pm 10.1\%$ for those without, $p = 0.0005$). Our group [7] has recently investigated changes in the mpMRI appearance of lesions on AS and showed the variability of volume measurements on serial scans, assessing change in lesion size according to grade. From a total of 86 men, 43/86 men did not have a visible lesion on the initial scan; of these, 5/43 had developed a suspicious focus at a median follow up of 3.6 years. There was a significant increase in volume by a median of 10% ($p < 0.01$), more specifically by a median of 6% for Gleason 3 + 3 and 18% for Gleason 3 + 4 ($p = 0.058$).

A recent meta-analysis by Schoots and colleagues [9] has shown that cancer upgrading occur almost three-times more often in men with a visible lesions (35%, confidence intervals -CI- 27–43%) in contrast to a negative scan (12%; CI 8–18%) with a relative risk of 2.77 (CI 1.76–4.38).

Gallagher and colleagues [8] reported the outcomes from a mpMRI based AS programme that did not involve protocol biopsies after the first confirmatory biopsy. In 211 men (median follow up of 4.2 years) progression to radical therapy was significantly higher at all stages in men with visible lesions than in men with initially negative scans (47/125 vs 11/86; $p < 0.001$).

Whilst there is a well-established reporting system for reporting mpMRI in the diagnostic setting (Prostate Imaging Reporting and Data System – PI-RADS v.2 and 2.1) [10,11], the challenge of assessing change over time needs addressing [12].

An international consensus panel has published the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) recommendations [13], which establish the reporting standards for mpMRI in men with PCa on AS.

These guidelines propose that mpMRI data should be collected and analysed in a standardised manner, including accurate size measurements of lesions over time. Moreover, a standardised, structured report should be generated for each scan, as well as the comparative reports over time.

Given the increasing burden in prostate mpMRI reporting that the radiologist faces, reporting according to the PRECISE recommendations can be time-consuming during daily clinical practice. There is a strong need of specific tools to allow reading, archival and analysis of mpMRI in a timely and accurate way.

The aim of this paper is to provide initial evidence of the utility of a specific tool to report according to the PRECISE recommendations, and to show the importance of automated comparison between sequential mpMRI in the individual man with PCa on AS.

2. Materials and methods

This is a retrospective analysis of a prospective, double-blind, randomised clinical trial (MAPPED) approved by the Hammersmith & Queen Charlotte's & Chelsea Research Ethics Committee (UK) (09/H0707/84), and the Medicines & Health Regulatory Agency and registered on the European Clinical Trials register (EudraCT 2009-

102405-18) [14].

All patients gave written informed consent to participate in this study.

2.1. Patient selection

The initial population comprised 42 men with biopsy-proven PCa on AS randomised to 6 months of 0.5 mg daily dutasteride (a 5-alpha reductase inhibitor widely used for the treatment of lower urinary tract symptoms) or placebo, undergoing 3T mpMRI scans at baseline and 6 months. The MAPPED study used mpMRI-determined PCa volume as a primary endpoint, and the detailed protocol has been previously published [15].

From the initial database, we randomly identified 20 men (ten in the dutasteride and ten in the placebo arm) and retrieved the baseline and the 6-month mpMRI scans for each patient.

2.2. MR imaging technique

All patients underwent mpMRI using a 3T system (Magnetom Verio, Syngo MR B17; Siemens Healthcare, Erlangen, Germany) and a pelvic phased-array coil. All examinations included unenhanced axial, sagittal and coronal turbo spin-echo T2 weighted imaging and axial diffusion-weighted imaging (b values of 0, 100, 800 s/mm^2 and dedicated 0, 1400 s/mm^2 used for calculation of the ADC map), and dynamic-contrast enhanced sequences during intravenous injection of 0.1 mmol/kg of body weight of gadoterate meglumine (Dotarem®, Guerbet, Roissy, France) at a rate of 2 mL/s, in accordance with standard guidelines [16]. In the absence of contraindications, an intramuscular injection of 20 mg of scopolamine butylbromide (20 mg, Buscopan, Boehringer Ingelheim, Ingelheim, Germany) was administered.

2.3. Image analysis

A specialist radiologist (FG, with 5 years of experience in PCa mpMRI reporting) - blinded to prostate specific antigen (PSA) values and treatment allocation - analysed the images using two different software programs: 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).

To avoid any recall bias, the radiologist started each reporting session using one software program (for 10 patients) or the other (for 10 patients) as the first platform.

Tumour volume by planimetry in all sequences (T2-weighted, diffusion-weighted -DWI- and dynamic contrast enhanced -DCE- imaging) and lesion conspicuity on DWI (i.e. the mean ADC of the peripheral zone divided by the mean ADC of the tumour) were assessed at each time point, as previously reported [15,17]. Reporting time for each scan using both platforms was also recorded (this included the time to hand-draw the diagram by the radiologist and the time to check PSA levels and Gleason Grade at the end of the reporting session, performed by an independent operator).

The PRECISE reporting tool provided a dedicated workflow that led the radiologist to report according to the PRECISE recommendations using a step-by-step procedure. After an overall look at the different sequences on the same window (Fig. 1), the radiologist was asked to contour the prostate by planimetry and then any visible lesion(s) on T2-weighted, DWI and DCE sequences independently (Fig. 2). At the end of each workflow, clinical and imaging data (such as PI-RADS or Likert score, PRECISE score, extracapsular/seminal vesicles extension, parameters changed from the previous scan, etc.) were manually inserted and included in the final structured report. At the beginning of the reporting session for follow-up scans (6 months), the contours of the prostate volume were rigidly transferred from the baseline scan, with the radiologist being able to edit them if needed. Conversely, only a

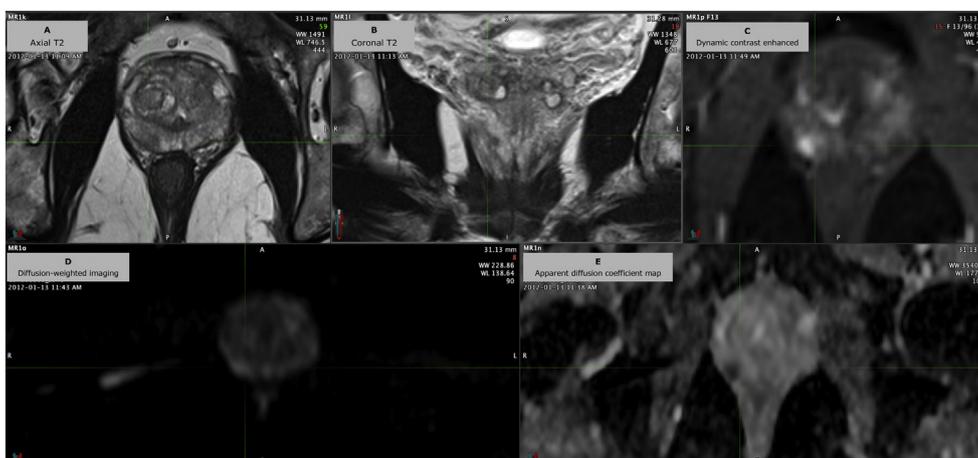


Fig. 1. Initial overview of the multiparametric MR scan using the PRECISE workflow.

single dot indicating the location of the previous lesion was transferred onto the new images to ensure an unbiased calculation of the new volume.

The conspicuity of each lesion was calculated after the reporting session, and therefore this was not included in the reporting time.

2.4. Statistical methods

Data are presented as medians and interquartile ranges (IQR) and were compared using a two-tailed Wilcoxon test. *P* values were then adjusted for False Discovery Rate and were considered to indicate a significant difference when < 0.05 .

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

3. Results

The median age of the 20 men analysed in this study was 63.45 years (IQR: 60.16–66.61), and median PSA at baseline was 6.3 ng/mL (IQR: 5.44–8.16). Twelve men (60%) had Gleason 3 + 3 and eight (40%) Gleason 3 + 4 PCa at entry biopsy.

All lesions (apart from one in the dutasteride arm that was not visible on DWI) were visible both at baseline and 6-month scans.

Table 1 reports median tumour volumes, ADC values and conspicuity calculated using the two software programs in the whole population ($n = 20$), both at baseline and after 6 months.

There were no significant differences between the two methods for all parameters.

There was a significant reduction in the reporting time at 6 months using the dedicated PRECISE reporting tool (12'33" vs 10'52", respectively; $p = 0.005$) (Table 1).

Similar results were found analysing the placebo ($n = 10$) and the

dutasteride ($n = 10$) arms independently, with no significant differences between the two methods for all parameters (Tables 2 and 3).

A significant difference in the reporting time was observed in the dutasteride arm using the PRECISE reporting tool (15'50" vs 12'59"; $p = 0.01$).

Additionally, a structured report including baseline and follow-up scans was generated using the dedicated tool, as advocated in the PRECISE recommendations [13] (Fig. 3).

Data obtained from the comparison between two-time points (including the increase or decrease rate) were also reported (Fig. 3).

A prose and a diagrammatic report from the same patient are shown in Fig. 4.

4. Discussion

The PRECISE recommendations were built to allow robust data collection of prostate mpMRI on AS and highlighted the areas most in need of research [13].

Our initial study indicates that a dedicated PRECISE software program is a promising tool to assist the radiologist in the reporting of serial prostate scans in men on AS for PCa.

Quantitative data extracted using the two platforms were comparable, as the volumes, ADC values and conspicuity were not significantly different (Table 1). Conversely, there was a significant reduction in the reporting time at follow-up scans using the dedicated PRECISE workflow, both for the whole population ($p = 0.005$) and in the dutasteride arm ($p = 0.01$).

The main reason lies in the capability of the PRECISE tool to transfer prostate volume contours from one scan to the other and to show the previous location of any lesion, with a considerable drop in the time required for contouring in the follow-up scan.

A closer look at the results in the dutasteride arm (Table 3) shows

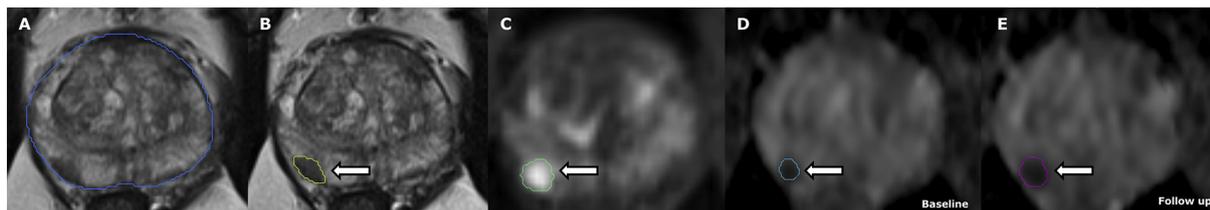


Fig. 2. Prostate volume (A) and lesion (B–E) contours by planimetry using the PRECISE workflow of a 59-year-old man with presenting PSA of 9.69 ng/mL and a Gleason 3 + 3 tumour at biopsy. This patient was in the placebo arm.

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).

Table 1

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) ^a	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 ^a ($\times 10^{-3}$ 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 ^a ($\times 10^{-3}$ 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 ^b	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.

^a Data from 19 patients.

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

Table 2

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 ^a ($\times 10^{-3}$ 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 ^a ($\times 10^{-3}$ 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 ^a	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.

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

Table 3

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) ^a	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 ^a ($\times 10^{-3}$ 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 ^a ($\times 10^{-3}$ 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 ^b	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.

^a Data from 9 patients.

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

that dutasteride was associated with increased tumour ADC and reduced conspicuity on DWI using both platforms. This is in line with our previous findings [17] and could also explain why the reporting time at 6 months was quicker using the PRECISE tool in this arm compared to the placebo (i.e. the lesion was less visible, and therefore less time was required to report the scan).

In addition to this, the PRECISE tool generated a structured report that compares data at different time points, including clinical and quantitative findings (Fig. 3).

This preliminary study suggests that the use of dedicated reporting tools in line with the PRECISE recommendations [13] could be of help

to report and analyse data from prostate mpMRI on AS and would allow to transfer contours and regions of interest to serial scans for quick comparison.

Moreover, specific tools to analyse data from different cohorts on AS could pave the way to the creation of a cloud-based platform for multiple centres with multiple readers, as advocated by the panel of experts who drafted the PRECISE recommendations [13].

Another key point that emerges from the PRECISE guidelines is the quality and standardisation of the mpMRI reports for men on AS. At present, many centres worldwide are still using a narrative report, often without including any images (Fig. 4). Such reports can vary from

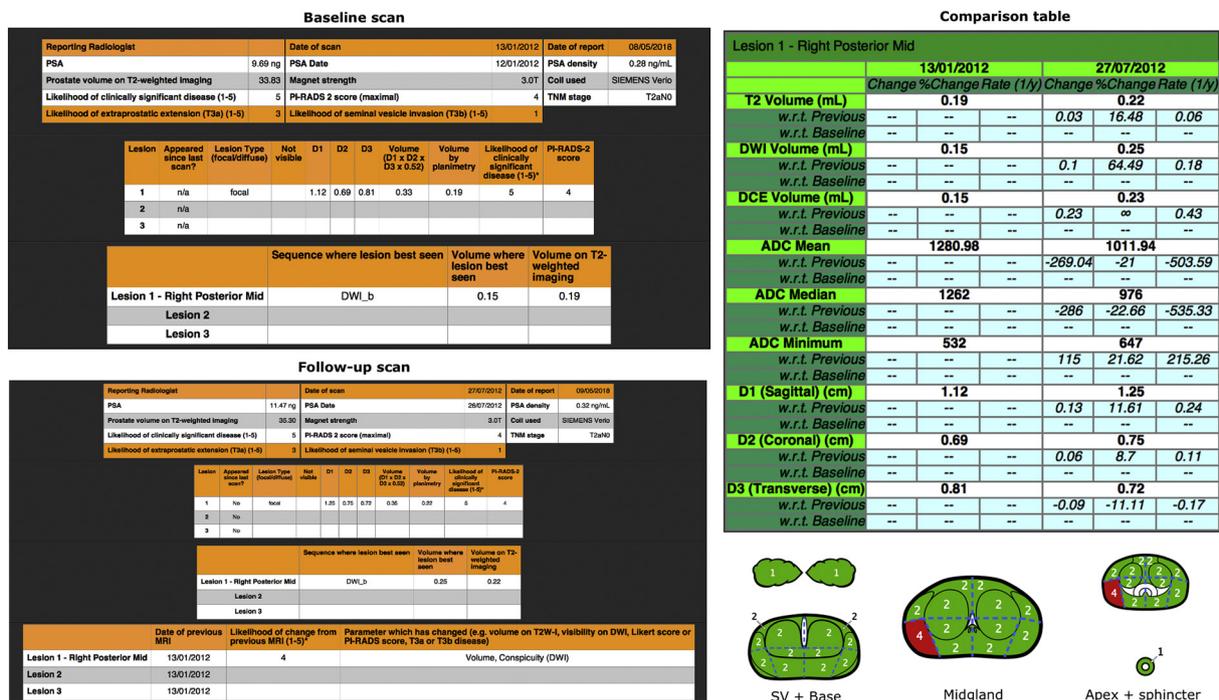


Fig. 3. Structured reports using a dedicated reporting tool according to the PRECISE recommendations of the same patient shown in Fig. 2. The images show data from baseline and follow-up scans together with a comparison table (including the rate of increase/decrease) of the key parameters of the lesion from each scan and a diagram showing lesion location and PI-RADS v.2 score (in red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

centre to centre and from radiologist to radiologist, resulting in a huge variability that can be sometimes difficult to interpret.

At this regard, the PRECISE recommendations suggest that the ideal report should be easily readable by different operators and should include the essential snapshots of the lesion on different mpMRI sequences, and a visual diagram that could assist the operator during biopsy procedures.

Our study provides a first attempt to address this issue, as we generated a structured report according to the PRECISE recommendations (Fig. 3).

It is clear from this study that dedicated platforms developed within the industry hold promise to analyse large data sets from men on AS for PCa allowing a quicker assessment and refinement of the PRECISE recommendations from multiple centres worldwide. Additionally, such platforms would aid quantitative analysis and structured reporting using fully automated and semi-automated algorithms in line with the PRECISE guidelines.

The correlation of radiological findings (both qualitative and quantitative) obtained from the PRECISE reporting tool with other clinical data (e.g. PSA) has been also advocated, and this has been

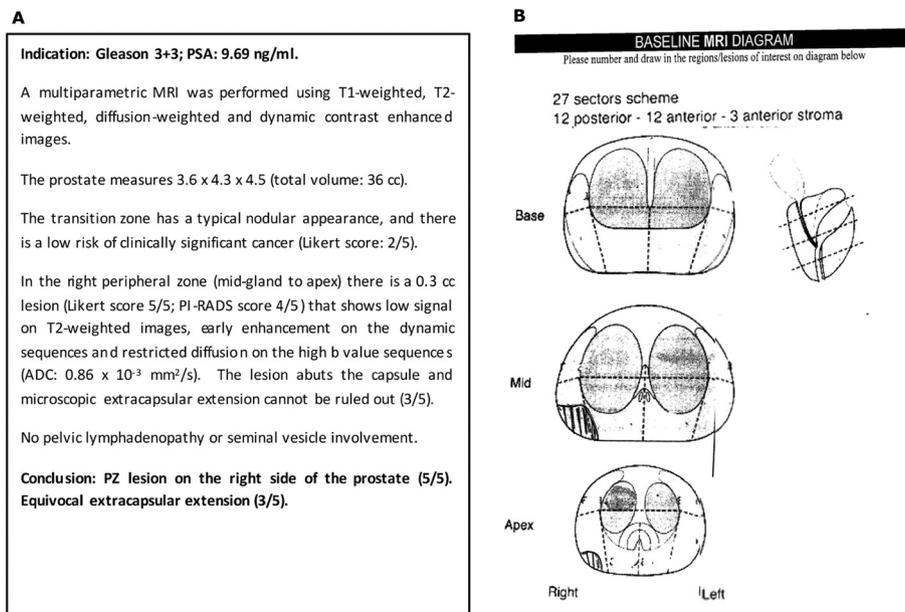


Fig. 4. Examples of a traditional prose (A) and hand-drawn diagrammatic (B) report of the same patient shown in Fig. 2.

included in the structured report that we obtained using our tool (Fig. 3).

The main finding of this study is that the use of a dedicated PRECISE reporting tool would facilitate the determination of thresholds that identify radiologically important changes on mpMRI on a large-scale, allowing men at lowest risk to have less frequent testing (with a positive impact on cost effectiveness for health systems) but at the same time ensuring that any signs of higher risk disease based on mpMRI phenotype can be carefully investigated (e.g. targeted biopsy). The comparison table (including the rate of increase or decrease of each parameter) shown in Fig. 3 represents a first answer to define these thresholds, which could be then compared with the histological outcomes from targeted biopsy if radiological progression is suspected.

Various methodological limitations apply to our study. First is the small cohort of men.

Second, we analysed only two mpMRI scans within a relatively short time frame (6 months), therefore we cannot comment on the medium/long-term natural history of PCa on mpMRI.

Third, a single radiologist was involved in this retrospective analysis and this does not allow assessing the inter-reader variability.

The same mpMRI machines were used for baseline and follow-up scans; therefore, we cannot comment on the variability between different systems and vendors.

Finally, we carried out our analysis using only two platforms, but we acknowledge that there are other commercially available platforms. It will be interesting to compare our results with those from other dedicated reporting platforms.

5. Conclusions

In conclusion, there is compelling evidence to support the use of mpMRI in men with PCa suitable for AS. However, there is still need of robust data from large cohorts that can provide a deeper insight into the huge amount of data that can be extrapolated from a single mpMRI scan. As such, there is a strong need of novel tools and reporting software programs to assist the radiologist in the reporting of sequential mpMRI scans according to the PRECISE recommendations [13]. If these recommendations will be widely used, the data derived will facilitate the determination of thresholds that identify radiologically significant disease and important radiologic changes on mpMRI.

To achieve this, automated comparisons across a patient over time using dedicated reporting tools would help with our understanding of the natural history of mpMRI changes on AS.

Our initial results support this idea and demonstrate how specific reporting programs can be of huge help to analyse large data sets, allowing a quicker assessment and refinement of the PRECISE recommendations.

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