

Title:

Role of MRI in low risk prostate cancer - finding the wolf in sheep's clothing or the sheep in wolf's clothing?

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Abstract (200 words)

Purpose of review:

In men on active surveillance for localised prostate cancer, MRI and MRI-targeted biopsies can be used prior to confirmatory or surveillance biopsy, to detect men with high-grade cancer (the wolf in sheep's clothing). In addition, some men will have low-risk disease despite adverse MRI findings (the sheep in wolf's clothing). We review the added value of image-guided biopsies in comparison to systematic TRUS-guided biopsies, using pathological reclassification as an end-point.

Recent findings:

At confirmatory and surveillance biopsies, both the MRI-targeted and repeat standard biopsies have shown value in identifying histological adverse findings in men with low-risk prostate cancer. For maximal detection of clinically significant cancer, a pre-biopsy MRI should be performed together with both MRI targeted and systematic TRUS-guided biopsies. Stable disease on MRI, may reduce the need for serial biopsies in some men on active surveillance.

Summary:

Prostate MRI and subsequent MRI-targeted biopsies are of value to the current management of men with low-risk prostate cancer on active surveillance. Prostate MRI, in combination of multivariable risk-prediction models within the near future, may help in identifying both the wolf in sheep's clothing and the sheep in wolf's clothing, and in potentially reducing serial biopsies.

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Keywords (max 5):

MRI, prostate cancer, active surveillance, biopsies, systematic review, monitoring, risk prediction.

Introduction

Active surveillance (AS) involves avoiding or deferring treatment in patients with very-low or low-risk prostate cancer, where treatment is proposed only if there is evidence of cancer progression. AS has become a standard management strategy, given the substantial morbidity of active treatments and the increasing evidence that very-low and low-risk prostate cancer are associated with negligible prostate cancer specific mortality [1, 2]. The aim in AS is to identify the prostate, which harbours higher risk disease, despite an initial standard biopsy showing low-risk disease (the wolf in sheep's clothing) (Figure 1). In addition, we know that due to the presence of inflammation or atrophy, some low volume or low-grade histological lesions can appear more aggressive on MRI (the sheep in wolf's clothing) (Figure 2).

It is usually recommended that men suitable for AS based on the findings of a first transrectal ultrasound (TRUS)-guided biopsy, undergo a confirmatory biopsy within one year, and then regular surveillance (follow-up) biopsies [2]. Unfortunately, the sensitivity of TRUS-guided biopsy is known to be low, especially in the case of anterior tumours or large prostates [3-5]. Biopsies directed to MRI lesions can detect aggressive prostate cancer more reliably than standard TRUS biopsies [6]. The purpose of this review is to evaluate the added value of multiparametric MRI (mpMRI) for the selection of patients for AS and during their follow-up, i.e. to define if mpMRI is useful in monitoring the herd of sheep and in discovering hidden wolves.

Objective

To perform a critical analysis of the published data of men eligible for AS in which mpMRI and MRI-targeted biopsies were used at confirmatory and surveillance biopsy, in addition to systematic TRUS-guided biopsies.

MRI imperfection

A recent systematic review reported studies of men who had radical prostatectomy despite suitability for AS on TRUS-guided biopsy findings (Gleason 3+3 alone). Of 677 men with a positive pre-operative mpMRI, 291 (43%) were upgraded to Gleason 3+4 or higher. Men with a negative mpMRI had a lower upgrade rate (78/293, 27%) [7].

There is discussion about whether all Gleason 3+4 cancers represent disease, which is likely to have clinical significance in a man's lifetime, particularly if it is of small volume. However, there is more agreement that T3 disease is likely to be significant in a man who is otherwise healthy. Upstaging to \geq T3 at radical prostatectomy in these men eligible for AS in this report occurred in 10% (54/557) following a positive pre-operative mpMRI, and in 8% (16/194) following a negative pre-operative mpMRI, showing little utility for mpMRI in predicting upstaging in this setting.

One of the significant factors here may well be that men had mpMRI after prostate biopsy, when it is known that artefact can lead to under and overstaging [8]. A small study of serial mpMRI, done prior to baseline at and intervals up to 6 months, showed that a minority of men will show changes on T2-weighted imaging, which can be interpreted as higher stage disease, for some time after T1-weighted biopsy artefact has settled, which may show a sheep in wolf's clothing [9].

Added value of mpMRI in men eligible for AS

For this review we focussed on patient cohorts of men with low-risk or very low-risk prostate cancer with no Gleason 4 component, based on systematic TRUS-guided biopsies. We assessed upgrading defined by Gleason \geq 3+4. The added value of mpMRI was defined as the additional upgrading due to mpMRI and targeted biopsy alone in addition to systematic TRUS-guided biopsy.

When analysing the added value of mpMRI, we focussed on the total cohort of patients undergoing an mpMRI, including the positive (Likert/PI-RADS score \geq 3) but also the negative mpMRI's. The explanation for this strategy is, that focusing only on

positive mpMRI's will favour the diagnostic test results of mpMRI significantly; by excluding men with negative mpMRI the cohort will be reduced significantly, but also the false negatives will be excluded, influencing the sensitivity, specificity and negative predictive value.

Added value of mpMRI and targeted biopsies at diagnostic biopsies

Only one prospective two-centre study used mpMRI prior to biopsy [10]. It reports 281 biopsy-naïve patients who had pre-biopsy mpMRI followed by 12-core systematic TRUS-guided biopsy, and who were eligible for AS, based on the systematic TRUS-guided biopsy findings. Fifty-eight percent of the patients (163/281) had a positive mpMRI and these men also underwent targeted biopsy during the same biopsy session. Patients were excluded from AS based on the finding of any Gleason $\geq 3+4$ or any biopsy core of Gleason $\geq 3+3$ with a > 5 mm cancer core length. Based on this definition, 10% of men (28/281) were reclassified by mpMRI-targeted biopsy as not eligible for AS. Based on the outcome definition of only Gleason $\geq 3+4$, only 3% (8/281) of men eligible for AS would be reclassified at the initial diagnosis of low-risk prostate cancer.

Added value of mpMRI and targeted biopsies at confirmatory biopsies.

In total 13 studies report on mpMRI at confirmatory biopsies (within one year of initial diagnosis) [11-23]. Four of these 13 studies showed only combined data of systematic and targeted biopsies at confirmatory biopsies [11-14], hence the added value of mpMRI could not be analysed; pooled data showed a reclassification rate of 22% (271/1255), based on Gleason 3+4 or higher .

One group updated their series in 2015 [19]. Therefore we excluded the report of 2014 [15]. Another group published twice on this topic between 2012 and 2015, however without overlapping recruitment periods, and were therefore both included [16, 18]. One of the studies did not explicitly mention whether these data refer to confirmatory biopsies only, or a mixture of confirmatory and surveillance biopsies [16]. We decided to include these data into our analysis.

In total, eight studies showed individual data on systematic TRUS-guided biopsies and MRI-targeted biopsies (Table 1) [16-23]. Pooled data showed a positive mpMRI in 73% (684/931), and a reclassification rate in 32% (297/931). Cancer upgrading occurred in 13% (121/931) in both systematic and targeted biopsies, whilst an

additional 11% (105/931) had upgrading on systematic biopsy alone, and 8% (71/931) on MRI-targeted biopsy alone. Thus, we believe that a pre-biopsy mpMRI should be performed at confirmatory biopsies, together with MRI-targeted biopsies if indicated.

Added value of TRUS-guided biopsies to mpMRI and MRI-targeted biopsies at confirmatory biopsies.

Surprisingly, the added value of TRUS-guided biopsies to the mpMRI and MRI-targeted biopsies was 11% (Table 1). In other words, 11% out of the total 32% reclassified men were missed by mpMRI and MRI-targeted biopsies. This higher percentage could be partly explained by the extra 3% (28/931) upgrading in the patients who had a negative mpMRI, but who underwent systematic TRUS-guided biopsies only. Thus, we believe that at present, systematic TRUS-guided confirmatory biopsies should still be undertaken irrespective of the pre-biopsy mpMRI results.

Added value of mpMRI and MRI-targeted biopsies at surveillance biopsies.

At surveillance biopsies (> 1 year follow-up in AS program) the added value of mpMRI can be based on studies with or without the use of a prior mpMRI at previous biopsies (at diagnosis, confirmatory or previous surveillance biopsies). We identified one study presenting data on mpMRI and surveillance biopsies without the use of previous mpMRI's [22] (Table 1). This cohort of men showed 45% (103/230) positive mpMRI's, with 17% (38/230) reclassification following the combined biopsy techniques. Cancer upgrading occurred in 1% (3/230) in both systematic and targeted biopsies, whilst an additional 13% (31/230) had upgrading on systematic biopsy alone, and 2% (4/230) on MRI-targeted biopsy alone. In this cohort, the added value of mpMRI at surveillance biopsies was limited.

We further identified four studies reporting data on surveillance biopsies with serial mpMRI's; these patients initially underwent pre-biopsy mpMRI followed by targeted and systematic biopsies [20, 24-26]. One group updated their series in 2016 [26], and we therefore excluded the report of 2015 [20]. Another study reported on men with serial mpMRIs and follow-up biopsies, but not explicitly mentioning this patient cohort was on active surveillance [24]. We decided to include this study. Surprisingly, a reclassification rate of 30% (81/269) was demonstrated following both MRI-targeted

and systematic TRUS-guided biopsies despite mpMRI and targeted biopsies previously (Table 2).

These findings are based on a small number of patients and must be interpreted with care. However, they suggest that 1) men eligible for AS, based on the combination of serial MRI targeted and systematic TRUS-guided biopsies, still harbour or develop high-grade prostate cancer during the course of AS (the wolfs in sheep's clothing); 2) both MRI-targeted and TRUS-guided biopsies show added value at surveillance biopsies, and should therefore be obtained both at surveillance/ follow-up biopsies.

Factors influencing the added value of MRI

The timing of offering active treatment is probably the biggest challenge in monitoring men under AS. This is traditionally done based on one of three factors: histological, biochemical or patient preference. The histological factors that might influence such a decision include the finding of higher Gleason grade, higher maximum percentage core involvement or an increase in the number of biopsies in a standard set of 10-12.

The use of MRI-targeted biopsy can affect each of these histological parameters and can result in so called 'risk inflation' where a cancer that is stable may be more accurately sampled at MRI-targeted biopsy and found to include higher risk features than when it was sampled in a systematic manner. It would be wrong to falsely encourage men to cease AS because of an apparent increase in risk (reclassification) rather than a true change in their cancer [27]. However, appropriate risk thresholds are not fully understood when MRI-targeted biopsies are used.

AS eligibility and study outcome threshold.

Some authors have advocated the inclusion in AS programs of (low volume) Gleason 3+4 cancers [28, 29]. Using Gleason $\geq 4+3$ instead of Gleason $\geq 3+4$ to trigger active treatment may change the added value of mpMRI. Tran *et al* showed data from which we could recalculate the added value of MRI-targeted to TRUS-guided biopsies depending on the threshold used for triggering active treatment [28]. The additional detection of Gleason $\geq 3+4$ using MRI-targeted biopsy is 14%, with a similar rate (13%) for Gleason $\geq 3+4$ detected on systematic biopsy and missed on MRI-targeted biopsy. Increasing the threshold, the additional detection of Gleason $\geq 4+3$ using MRI-targeted biopsy is 8%, in contrast to 4% detected on systematic biopsy and missed on MRI-targeted biopsy.

Increasing the threshold may show a relative higher added value for mpMRI and MRI-targeted biopsies in comparison to the TRUS-guided biopsies. However, increasing the threshold of AS eligibility is still controversial. Although AS could be performed with more confidence with the use of both biopsy strategies, men with initial Gleason 3+4 were 4.6 more likely to have upgrading at 3 years than men with initial Gleason 3+3 ($p < 0.01$) [29]. In addition, 63% of men on AS with initial Gleason 3+4 had upgraded by the third surveillance year, compared with 18% of men starting with Gleason 3+3 ($p < 0.01$).

MRI suspicion score threshold.

The Likert scale asks a radiologist to score the likelihood of clinically significant disease based on their overall impression of all the sequences; the more formal PI-RADS (Prostate Imaging and Report and Data System) defines criteria for each score 1-5 for each of the multi-parametric sequences. There is ongoing debate about which may be more accurate.

In most studies mpMRI lesions with a Likert/PI-RADS score $\geq 3/5$ are targeted at biopsy. Using a threshold score of $\geq 4/5$ will lower the reclassification rate for the mpMRI and MRI-targeted biopsies, as the equivocal lesions (score 3) are not biopsied. However, around one quarter of men scoring equivocal on mpMRI will have upgrading to Gleason 3+4 or higher in some series [15, 19, 21]. Further developments and adjustments to the PI-RADS scoring system may decrease the amount of detected high-grade prostate cancers in this equivocal category [30].

MRI as a monitoring tool.

Preliminary results suggest a negative mpMRI is a predictor of excellent prognosis during AS [31]. Small index lesions on mpMRI may correspond to benign lesions or indolent cancers based on grade and size [32]. If this is confirmed, an mpMRI with negative findings or small index tumour may allow a reduction in the frequency of surveillance biopsies. In addition, changes in size or appearance of the mpMRI lesion(s) may predict upgrading and trigger biopsy.

In an international effort set up by the European School of Oncology, to collect robust evidence in this area, recommendations have been developed to collect data in men having mpMRI on AS (PRECISE criteria - prostate cancer radiological estimation of change in sequential evaluation) [33]. Data that should be recorded include the absolute

size of a lesion at baseline and follow-up, the MRI suspicion score (Likert or PI-RADSv2) and the likelihood of progression being present. There is debate about whether volume measurements or single or dual parameter measurements are more accurate in assessing changes in volume over time. Further data is required to assess this robustly. Likelihood of radiological progression (scored on a 1-5 Likert scale) should be based on a significant increase in size or conspicuity of a known lesion, the appearance of a new lesion, or definitive evidence of stage progression such as extraprostatic extension, seminal vesicle involvement, lymph node involvement, or bone metastasis.

A few studies have reported data on sequential mpMRI evaluation [20, 24-26]. They considered an increase in suspicion score or lesion diameter as a sign of progression. Two studies also used the additional criterion of developing new suspicious lesions in comparison to initial MR imaging, and one study used a decrease of ADC value of more than 150 mm²/s.

In these surveillance cohorts the overall upgrading from Gleason 3+3 into Gleason \geq 3+4 was 30% (81/269), following the combined targeted and standard biopsies (Table 2). When stratifying into the categories of 'MRI progression' and 'MRI regression or stable', upgrading occurred in 39% and 21%, respectively. Although upgrading was more likely in men with a change on mpMRI, there was still a significant proportion of men who were upgraded despite a stable MRI. We suggest that stable disease on prostate mpMRI may not justify omitting repeat targeted and systematic biopsies.

Adding MRI to current risk calculators

Models to predict upgrading at repeat biopsy using a combined approach of clinical parameters together with standard and MRI-targeted biopsies have been published in men having confirmatory biopsies [4, 14]. In a validation cohort of 85 men on AS, this model could have safely avoided 27–68% of biopsies, depending on the cut-off point of the biopsy threshold, and depending on the tolerance for missing higher grade disease [22]. Given the slow growth of most prostate cancers, a relatively higher tolerance for missed high-grade disease would be justifiable since the number of risk features for the lesion is likely to increase on prostate mpMRI with time. In men on AS, independent risk predictors of upgrading have shown to be Gleason 3+4 and PSA density > 0.15 ng/ml/cm³, MR imaging related risk predictors have shown to be ADC values below

1000 mm²/s and an mpMRI lesion score of 5 [28, 29, 34, 35]. Including mpMRI in multivariable risk-prediction models could help in identifying men on AS at risk of high-grade prostate cancer, i.e finding the wolfs in sheep's clothing.

Conclusion:

MR imaging improves patient selection for active surveillance and is useful in follow-up during active surveillance. At present, many centres using MRI-targeted biopsies will also perform systematic biopsies during follow up, and current data supports this.

Prostate mpMRI as a monitoring tool in men under Active Surveillance is an emerging field and stratifying men into those showing 'MRI progression' and 'MRI stable/regression', may be useful and may decrease the requirement for repeat biopsies in some men.

Combining mpMRI with multivariable risk-prediction in men on active surveillance may seem the way forward, helping in identifying both the wolf in sheep's clothing and the sheep in wolf's clothing, in reducing (serial) biopsies, in choosing a biopsy strategy or additional diagnostic approaches, and finally in counselling the patient adequately and with more confidence to active surveillance or active treatment.

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3-5 key bullet points that summarise the article

- In men on active surveillance mpMRI should be used prior to confirmatory or surveillance biopsy
- Most centres using mpMRI and MRI-targeted biopsies continue to use standard biopsy
- A stable mpMRI, in conjunction with other parameters may be helpful in avoiding repeat biopsy in some men, with appropriate counselling
- New definitions of risk are needed for an MRI-targeted approach

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Table 1. Added value of MRI and MRI-targeted biopsies (MRI-TBx only) and TRUS-guided biopsies (TRUS-Bx only) in upgrading at confirmatory and surveillance biopsies of men on active surveillance

Included studies	Year	AS criteria, based on TRUS-Bx only	Reclassification criteria	Patients (denominator)	Positive MRI (numerator)	%	Upgrading at biopsy									
							Total (numerator)	%	MRI-TBx only (numerator)	%	TRUS-Bx only (numerator)	%	MRI-TBx and TRUS-Bx (both) (numerator)	%	TRUS-Bx only in negative MRI (numerator)	%
Confirmatory biopsy																
Margel [16]	2012	Epstein	GS≥3+4, >2 +cores, or ≥50% CCL	56	34	0,61	20	0,36	2	0,04	8	0,14	10	0,18	2	0,04
Marliere [17]	2014	Epstein	GS≥3+4	41	24	0,59	23	0,56	9	0,22	14	0,34	0	0,00	5	0,12
Da Rosa [18]	2015	GS≤6	GS≥3+4	72	54	0,75	19	0,26	7	0,10	2	0,03	10	0,14	2	0,03
Kamrava [19]	2015	GS≤6	GS≥3+4	245	176	0,72	63	0,26	11	0,04	32	0,13	20	0,08	10	0,04
Walton Diaz [20]	2015	Epstein	GS≥3+4	152	120	0,79	34	0,22	12	0,08	10	0,07	12	0,08	1	0,01
Recabal [21]	2016	GS≤6	GS≥3+4	206	135	0,66	72	0,35	15	0,07	25	0,12	32	0,16	8	0,04
Ma [22]	2016	GS≤6	GS≥3+4	54	54	1,00	12	0,22	3	0,06	6	0,11	3	0,06	n.a.	
Pessoa [23]	2016	Epstein, ≤3 +cores	GS≥3+4, ≥3 +cores, or >50% CCL	105	87	0,83	54	0,51	12	0,11	8	0,08	34	0,32	0	0,00
<i>Pooled data</i>				931	684	0,73	297	0,32	71	0,08	105	0,11	121	0,13	28	0,03
Surveillance biopsy																
Ma [22]	2016	GS≤6	GS≥3+4	230	103	0,45	38	0,17	4	0,02	31	0,13	3	0,01	13	0,06

Inclusion criteria to active surveillance were based on GS 3+3 or (modified) Epstein criteria (≤cT2a, PSA <10, GS 3+3, ≤2 positive cores, <50% CCL), obtained by systematic TRUS-guided biopsies. Upgrading was based on the outcome definition of GS ≥3+4 (with 2 studies also upgrading if >2 positive cores, or >50% cancer core length). Extracted MRI-targeted biopsy data was from lesions with a suspicion score 3-5 (Likert/PI-RADS).

Denominator = no. of patients, numerator = no. of reclassified patients (total, MRI-TBx only, TRUS-Bx only, both MRI-TBx and TRUS-Bx, TRUS-Bx only in negative MRI).

GS, Gleason score; MRI, magnetic resonance imaging; TRUS, transrectal ultrasound; Bx, biopsy; TBx, targeted biopsy; CCL, cancer core length

Table 2. Upgrading data at surveillance biopsies in men on active surveillance, stratifying into 'MRI progression' and 'MRI stable or regression'

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Included studies	Year	No. Patients with positive MRI (denominator)	Upgrading at surveillance biopsy									
			Upgrading		Progression on MRI		Upgrading		Regression or stable on MRI		Upgrading	
			No.	%	No.	%	No.	%	No.	%	Total	%
Rosenkrantz [24]	2015	55	13	0,24	23	0,42	8	0,35	32	0,58	5	0,16
Felker [25]	2016	48	19	0,40	10	0,21	7	0,70	38	0,79	12	0,32
Frye* [26]	2016	166	49	0,30	107	0,64	39	0,36	59	0,36	10	0,17
Pooled data		269	81	0,30	140	0,52	54	0,39	129	0,48	27	0,21

* included men with mpMRI suspicion score low (PI-RADS 1-2), moderate (PI-RADS 3), high (PI-RADS 4-5)

MRI, magnetic resonance imaging; TRUS, transrectal ultrasound;

Figures 1. Wolf in sheep's clothing.



Figure 1a. Wolf in sheep's clothing.

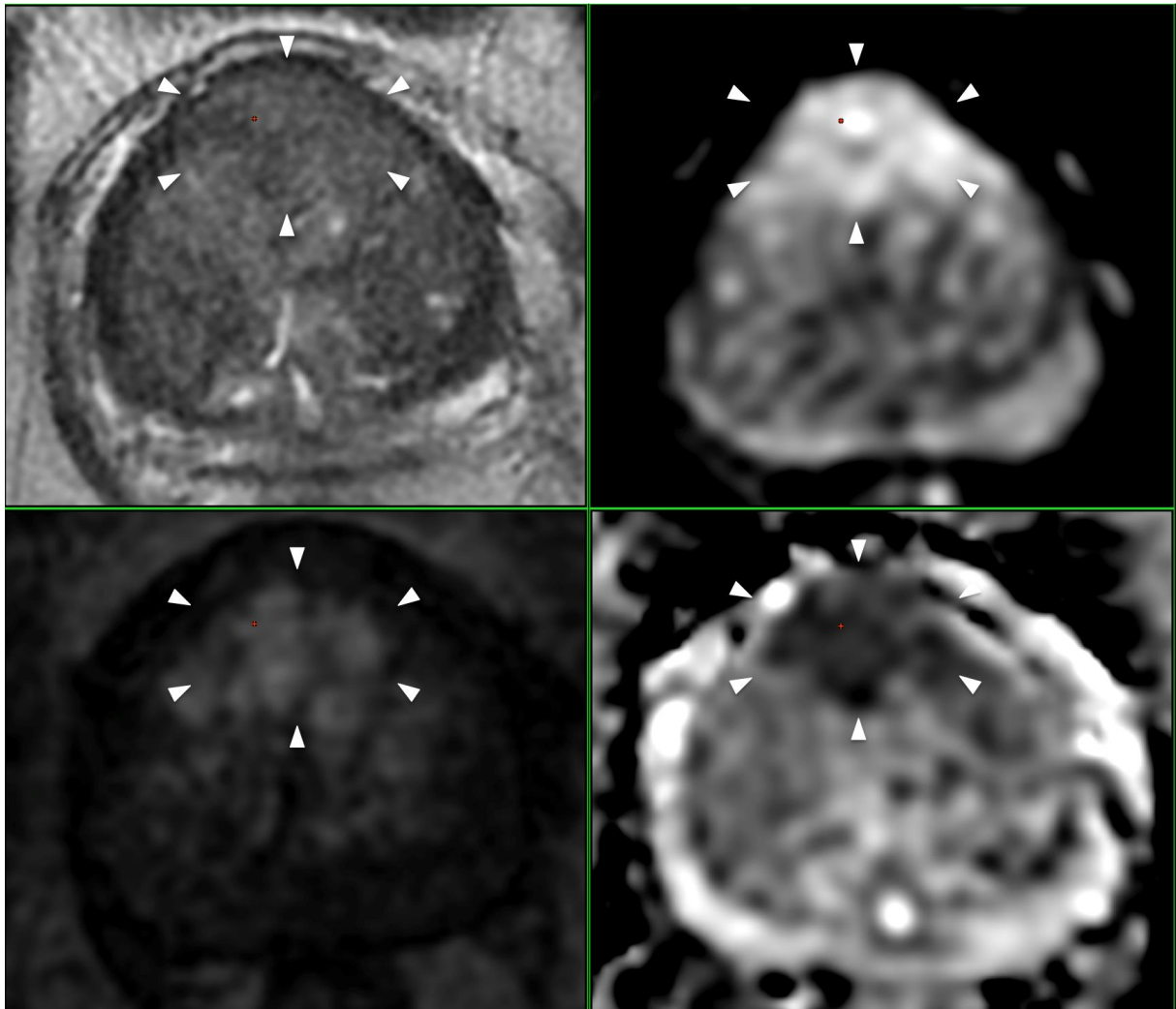


Figure 1b.

A 73-year-old man on active surveillance for Gleason 3+3 tumor (1 positive core out of 10 biopsies) on previous TRUS-guided biopsy. PSA increased during the last year, with a T1c on digital rectal examination. Multiparametric prostate MRI examination shows an elliptical focus of homogenous decreased T2 signal (A; axial T2w), increased DWI signal (B; axial DWI b-800), hypervascularity (C; axial DCE-MRI), and reduced signal on ADC (D; axial ADC map), within the anterior transition zone. Likert/PI-RADSv2 suspicion score 5. Subsequent MRI-US software fused targeted surveillance biopsies demonstrated a high-volume Gleason 3+4 tumor, not detected with systematic TRUS-guided biopsies.

Figure 2. Sheep in wolf's clothing



Figure 2a. Sheep in wolf's clothing

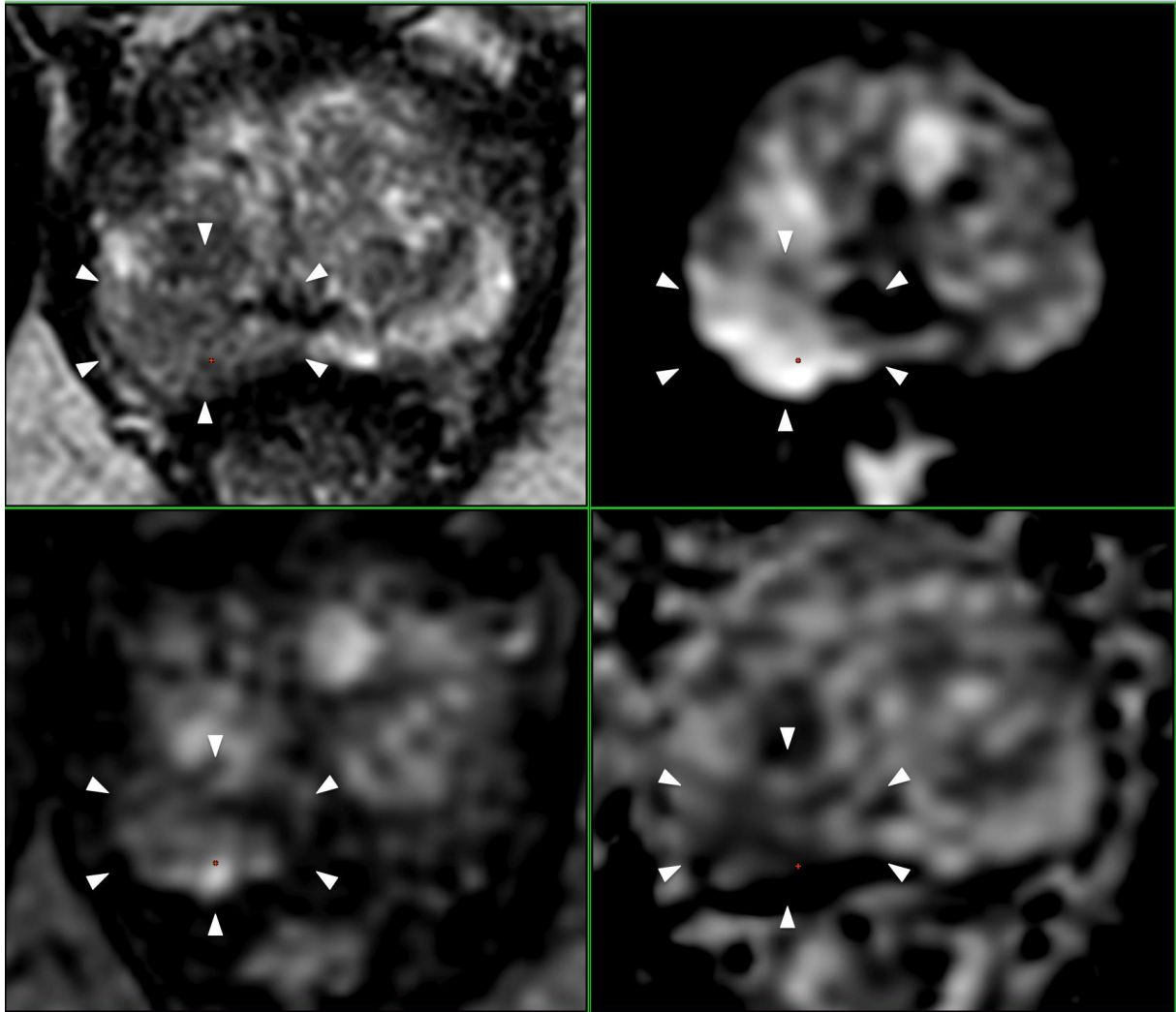


Figure 2b. A 59-year-old man on active surveillance for Gleason 3+3 tumor on previous TRUS-guided biopsy (1 positive out of 8 right sided). PSA increased during the last year, with a T1c on digital rectal examination. Multiparametric prostate MRI examination shows an elliptical focus of decreased T2 signal (A; axial T2w), increased DWI signal (B; axial DWI b-800), hypervascularity (C; axial DCE-MRI), and reduced signal on ADC (D; axial ADC map), within the right dorsolateral peripheral zone. Likert/PI-RADSv2 suspicion score 4. Subsequent MRI-US software fused targeted surveillance biopsies showed inflammation, however biopsies did not demonstrate any prostate cancer (0 positive cores out of 3). This suggests focal prostatitis, a mimicker of high-grade prostate cancer. Systematic TRUS-guided biopsies detected right-sided GS 3+3 prostate cancer (2 positive cores out of 8). Patient is still eligible for active surveillance.