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Interaction of MRI and active surveillance in prostate cancer: Time to re-evaluate the active surveillance inclusion criteria

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Abstract

Currently available data from long-running single- and multi-center active surveillance (AS) studies show that AS has excellent cancer-specific survival rates. For AS to be effective the 'right' patients should be selected for which up until 5-to-10 years ago systematic prostate biopsies were used. Because the systematic prostate strategy relies on sampling efficiency for the detection of prostate cancer (PCa), it is subject to sampling error. Due to this sampling error, many of the Gleason 3+3 PCas that were included on AS in the early days and were classified as low-risk, may in fact have had a higher Gleason score. Subsequently, AS-criteria were more strict to overcome or limit the number of men missing the potential window of curability in case their tumor would be reclassified. Five to ten years ago the prostate biopsy landscape changed drastically by the addition of magnetic resonance imaging (MRI) into the diagnostic PCa-care pathway, which has by now trickled down into the EAU guidelines. At the moment, the EAU guidelines recommend performing a (multi-parametric) MRI before prostate biopsy and combine systematic and targeted prostate biopsy when the MRI is positive (i.e. PIRADS ≥3).

So because of the introduction of the MRI into the diagnostic PCa-care pathway, literature is showing that more Gleason 3+4 PCas are being diagnosed. But can it not be that the inclusion of MRI into the diagnostic PCa-care pathway causes risk inflation, resulting in men earlier eligible for AS, now being labelled ineligible for AS? Would it not be possible to include these current Gleason 3+4 PCas on AS? The authors hypothesize that the improved accuracy that comes with the introduction of MRI into the diagnostic PCa-care pathway permits to widen both the AS-inclusion and follow-up criteria. Maintaining our inclusion criteria for AS from the systematic biopsy era will unnecessarily and undesirably expose patients to the increased risk of overtreatment. The evidence behind the addition of MRI-targeted biopsies to systematic biopsies calls upon the re-evaluation of the AS inclusion criteria and research from one-size-fits-all protocols used so far, into the direction of more dynamic and individual risk-based AS-approaches.

1. Introduction

Screening for prostate cancer (PCa) reduces PCa-specific mortality, but is associated with overdiagnosis and subsequent overtreatment of low-risk PCa [1]. In 2004 Parker argued that overdiagnosis by prostate specific antigen (PSA) screening would not matter if only treatment had no morbidity [2]. Unfortunately, treatment does result in morbidity and so we must either avoid overdiagnosis or reduce the harm by avoiding treatment-related morbidity. Active surveillance (AS) for men with low-risk PCa and a life expectancy >10 years was developed as an option to counteract the harms of PSA-based PCa screening. Instead of directly starting definitive treatment such as radical prostatectomy (RP) or radiotherapy (RT), men choosing an AS-strategy are being monitored and only switch to definitive treatment when signs of progression to higher risk disease are seen. AS can, however, only be effective in reducing the harms of screening when three prerequisites are met: (A) if we are able to select those men that have overdiagnosed cancer at entrance upon AS, whom are fit for and willing to undergo definitive treatment and have a life expectancy of >10 years. If not, men can enter watchful waiting which differs from AS in the sense that the aim of

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watchful waiting is to observe the PCa until it has metastasized or started to cause symptoms. At that point palliative treatment can be considered. (B) When it is possible to selectively filter out the men with signs of more aggressive disease during follow-up (i.e. before they miss their window of curability), and (C) when the monitoring protocol is not too demanding for a patient, i.e. does not result in stopping AS due to other than PCa-related issues [3].

Currently, AS is reducing overtreatment of overdiagnosed PCa's. Descriptive analyses of the worldwide AS cohorts included in the Movember GAP3 consortium showed that 43.6% of men drop-out of AS during the first 5 years of follow-up, predominantly due to signs of disease progression [4]. That percentage of 43.6% leaves room for improvements to be made in the inclusion and follow-up criteria of AS protocols and subsequently results in a decrease of the number of men having to switch to definitive treatment.

The incorporation of magnetic resonance imaging (MRI)-targeted biopsy in the diagnostic PCa-pathway is likely to influence the risk profile of patients diagnosed with PCa. Therefore, in this seminar article, the authors will reflect upon how a potential stage shift or risk inflation caused by the implementation of MRI at the detection of PCa may affect the inclusion of men on AS and how incorporation of MRI into AS follow-up schemes changes rates of reclassification and drop-out.

2. Long-term AS outcomes and inclusion of AS in the PCa guidelines

Long-running, single-institution studies investigating the effectiveness of AS monitoring protocols for low-risk PCa, such as the cohorts from The Johns Hopkins University and the Sunnybrook Health Sciences Center at the University of Toronto, have been publishing their results since 2002 [5,6]. In the Johns Hopkins cohort AS was offered to men with very-low or low-risk PCa, whereas the Sunnybrook cohort consisted of favorable and selected intermediate-risk patients [5,6]. Follow-up schedules consisted of PSA testing, rectal examinations, and systematic prostate biopsies. While the one follow-up protocol was more stringent than the other, the currently available long-term data from both cohorts shows that AS has excellent cancer-specific survival rates [7,8]. The Johns Hopkins cohort reported a cancer-specific survival rate of 99.1% and a metastasis-free survival rate of 99.4% at both 10- and 15-years of follow-up [7]. In the Sunnybrook cohort the cancer-specific survival rate was 98.1% after 10 years and 94.3% after 15-years of follow-up [8]. In this cohort, 2.8% developed metastasis after 15-years, and 1.5% died of PCa [8]. The risk of cancer death or metastasis in the Johns Hopkins cohort was <1% after 10- to 15-years of follow-up [9]. In 2006 the international, multi-center, web-based Prostate cancer Research International Active Surveillance (PRIAS) study was started. After 5- and 10-years of follow-up, 98% and 94% of men, respectively, were free of biochemical recurrence, local recurrence, metastasis, and PCa-death [10]. The other-cause mortality rates at 5- and 10-years after diagnosis were 3% and 11%, respectively. In the same follow-up periods, the disease-specific mortality rates were both <1% [10]. Based on, amongst others, these results AS has been included as the recommended treatment strategy for low-risk PCa in the international guidelines [11,12].

3. AS patient selection and MRI

For AS to be effective the 'right' patients should be selected – i.e. only the men in whom the cancer is not going to cause any symptoms or death during their expected life time. In the early days, the inclusion of patients on AS relied on the outcomes of, amongst others, systematic biopsies taken during the diagnostic process or as a confirmation shortly after inclusion on AS. Using this technique means that tissue cores are systematically obtained throughout the prostate. The contemporary systematic prostate biopsy strategy relies on sampling efficiency for the detection of cancer and is therefore subject to sampling error [13]. Sampling error refers to a false-negative biopsy or incorrect risk stratification because of undersampling, but also to the detection of clinically insignificant disease as a result of oversampling, as well as to the necessity for repetitive biopsy [13]. In some series, the false-negative rate of a 12-core extended biopsy exceeds 30% and undersampling of the prostate occurs in up to 30% of cases, which leads to clinically significant tumors being missed on initial biopsy [13-15]. Furthermore, undersampling leads to incorrect risk stratification. It is likely that many of the patients with low-risk PCa that were included on AS in those early days, may in fact have had a higher risk tumor. Because of the limitations of the contemporary systematic prostate biopsy technique, AS inclusion criteria had to be more strict. This means that the inclusion criteria also included prostate-specific antigen (PSA) cut-off levels, the PSA-density (PSA divided by prostate volume), a maximum number of positive biopsy cores, etc. This to overcome or limit, as much as possible, that men included on AS would miss the potential window of curability during AS follow-up in case their tumor would be reclassified. The published results of the Johns Hopkins, Sunnybrook and PRIAS active surveillance cohorts, have shown that this approach is highly effective [5-10].

In clinical practice, one would like to reach an optimal prostate biopsy strategy by balancing the adequate detection of clinically significant PCa (sensitivity), gaining confidence with respect to the accuracy of negative sampling (negative predictive value), limiting the detection of clinically insignificant cancers, as well as reaching good concordance with whole-gland surgical pathology results. This proper balance allows for accurate risk stratification for selecting a treatment [13]. Such an optimal biopsy strategy

would furthermore take into account both an appropriate number of biopsy cores and core location.

Five to ten years ago the prostate biopsy landscape changed drastically by the addition of MRI into the diagnostic PCa-care pathway. MRI contributes to the optimal prostate biopsy strategy through a more selective disease localization, which improves the risk stratification as well as the cancer detection rates and potentially reduces the number of biopsy cores taken [13]. Evidence regarding the accuracy of MRI-guided biopsies was published in series that were able to compare the outcomes of MRI-guided biopsies with radical prostatectomy (RP) specimens. Results showed that the risk of grade group upgrading on RP became smaller after combined MRI-targeted and systematic prostate biopsies versus systematic biopsies alone [16-21]. The MRI targeted biopsy approach improves the detection of clinically significant PCa compared to systematic prostate biopsy alone [22-25], and currently has the best diagnostic accuracy. Most studies agree on the improved detection rate of clinically significant PCa and the decreased rates of clinically insignificant PCa diagnoses by the MRI-targeted biopsy approach, although the evidence on the added value of systematic biopsy cores is still contradictory [20, 26]. This is reflected in the EAU guidelines on PCa which recommend to perform a (mp)MRI before prostate biopsy and combine systematic and targeted prostate biopsy when the MRI is positive (i.e. PIRADS ≥3) [11]. In men with previous negative biopsy and a persistent suspicion of PCa, targeted biopsy only is considered sufficient [11].

So because of the introduction of the MRI into the diagnostic PCa-care pathway we are better able to predict upfront which tumors are clinically insignificant (i.e. do not need immediate definite therapy) and which are clinically significant (i.e. do need immediate definite therapy). Together with the advancements in PCa pathology with respect to the presence of cribriform and/or intraductal growth patterns, literature is showing that more Gleason 3 +4 PCas are being diagnosed [20,25]. In the past it is likely that these now diagnosed Gleason 3+4 PCas were labelled as Gleason 3+3 PCa, due to systematic prostate biopsy sampling error. The suggestion therefore is that Gleason 3+4 PCas now diagnosed under the MRI diagnostic PCa-pathway will perform well on AS. In the Sunnybrook AS-cohort 25% of the patients fulfilled the D'Amico criteria for intermediate-risk PCa based on systematic prostate biopsy alone. Klotz et al. reported that the 15-year PCa-mortality was still low [8], however, that patients with intermediate-risk disease had a 3.7-fold greater development of metastases compared to men with low-risk disease [27]. Godtman at el. reported on intermediate- vs. low-risk PCa patients on AS in the screening arm of the Göteborg screening trial. While the 10-year failure free survival was lower for men with intermediate-risk PCa (73% vs. 85% for low-risk and 95% for very low-risk), the PCa-specific survival at 10 years was still very high (98% for intermediate- vs. 100% for low- and 100% for very low-risk PCa) [28]. The outcomes of both studies reflect the safety of AS in the pre-MRI era. Furthermore, Vickers et al., is rightfully arguing that MRI-detected lesions are not oncologically equivalent to those detected by systematic biopsy [29]; i.e. it are not more Gleason 3+4 PCas that are being detected, they are being called Gleason 3+4 PCas while before they were diagnosed as Gleason 3+3 PCas.

So the inclusion of MRI in the diagnostic PCa-care pathway is likely to cause risk inflation; because the accuracy of prostate biopsy has increased through the introduction of MRI-targeted prostate biopsy, men eligible for AS in the past, are now labeled as ineligible for AS. The question is whether that is justified. Would it not be possible to include these current Gleason 3+4 PCas on AS? It can be hypothesized that the improved accuracy may actually permit to widen the 'secondary' AS-inclusion and follow-up criteria, such as PSA-density and number of positive cores. Furthermore, it may be argued that also the 'primary' Gleason 3+3 inclusion criteria can be widened, to subsets of men diagnosed with a Gleason 3+4 PCa.

4. AS patient follow-up and MRI

MRI is not only used in the diagnostic phase of the PCa-care path, but also during follow-up of men on AS. In 2013 the PRIAS MRI side-study was initiated, in which patients with >2 cores positive for PCa are allowed and MRI is used before diagnosis and/or during follow-up [10]. The MRI side-study protocol recommends to perform an MRI with targeted prostate biopsies three months after the inclusion of a patient and in combination with the planned systematic prostate biopsies at year 1, 4, 7, and 10. If there was a diagnostic MRI available, then the MRI three months after inclusion on AS should be omitted. In case of a PSA doubling time of <10 years and the availability of a clinical use MRI, an annual MRI is recommended with targeted prostate biopsy only if the MRI shows progression. When the PRIAS study started-off in 2006, a switch to definitive treatment was advised if the PSA doubling time was <3 years, if >2 biopsy cores showed PCa, if Grade Group >1 was detected or if the digital rectal examination showed > cT2. The recommendation to switch to definitive treatment when the PSA doubling time was <3 years was removed in the PRIAS MRI side study. Also, when >2 biopsy cores showed PCa Grade Group >1, it was recommended to continue AS [10, 30]. Because the use of MRI has become standard clinical practice in most healthcare systems, the MRI has been incorporated into the PRIAS monitoring protocol as of 2021, in line with the criteria outlined above (www.prias-project.org). PRIAS is not the only study which has included the MRI in their monitoring protocol. For instance, the University College London Hospital (UCLH) AS-cohort has incorporated MRI into their AS program, as did the fifteen studies included in the recent systematic review on the

use of MRI to detect PCa progression during AS by Rajwa et al. [31, 32].

Luiting et al. reported on the outcomes of three subpopulations of PRIAS patients, namely; (1) a group of 500 patients diagnosed before 2009 without MRI before or during AS, (2) a group of 351 patients who were diagnosed without MRI, but who underwent an MRI within the first 6 months after diagnosis, and (3) a group of 435 patients who underwent MRI both before diagnosis and during follow-up [30]. Results showed that in the 'no MRI-group' the 2-year cumulative probability of discontinuing AS was 27,5% and that Grade Group reclassification accounted for 6.9% of the men discontinuing AS. In the 'MRI within 6 months after diagnosis-group' the 2-year cumulative probability of discontinuing AS was 30.9%, of which 22.8% could be accounted to Grade Group reclassification. Finally, in the 'MRI before diagnosis and during follow-up-group' it amounted to 24.2%, of which 13.4% could be accounted to Grade Group reclassification [30]. The results presented by Luiting et al. suggest that using MRI could lead to more patients being deemed unsuitable for AS.

5. AS adherence

The safety of AS depends, in part, on whether or not AS-participants follow the monitoring protocol, and adhere to the planned tests. Literature has shown that the adherence to AS protocols is currently suboptimal, especially when it comes to the adherence to the recommended prostate biopsy procedures [33]. Inclusion of the MRI may reveal to be more attractive to patients, as a negative MRI may lead to avoiding prostate biopsies. Such a protocol in which prostate biopsies may not be necessary if the MRI allows so, may be 'easier' and more 'patient-friendly' to adhere to. It should not be mistaken by the thought that it also causes less anxiety amongst AS-patients. The increased confidence of prostate sampling through the use of MRI may lead to a decrease in the AS anxiety-based discontinuation rates. During the Annual Congress of the European Association of Urology in 2015, Hamoen et al. presented the generic anxiety levels as measured by the 6-item State-Trait Anxiety Inventory (STAI-6) for a subsection of patients that were included in the PRIAS MRI side-study [34]. The results were compared to anxiety levels of men who underwent immediate definitive treatment and men who were managed with AS without mpMRI being used in the follow-up protocol. In total 99/111 (response rate 89%) men participated and completed the STAI-6 questionnaire. Twenty-five men were on the AS + mpMRI protocol, 28 men followed AS without mpMRI and 45 men underwent definitive treatment. The mean anxiety score was lower for men that were managed by AS with mpMRI as compared to men that underwent definitive treatment (28.8 vs. 30.8, $P = 0.341$). The difference in scores was not statistically significant and likely not to be clinically relevant [34]. In the study by Luiting et al., the opposite seemed to be true. In the 'MRI before diagnosis and during follow-up-group' the probability to discontinue AS because of anxiety was higher (3.6%, 95% CI 1.1 − 6.1%) as compared to the 'no MRI-' (1.8%, 95% CI 0.6 − 3.0%) and the 'MRI within 6 months after diagnosis-group' (1.8%, 95% CI 0.2 − 3.4%) [30].

6. Conclusions

In conclusion, for AS to be effective three prerequisites have to be met: (A) the 'right' patients should be selected, (B) more aggressive disease should be filtered out selectively during AS-follow-up, and (C) the monitoring protocol should not be too demanding for a patient. MRI can play an important role in all three elements. We have seen that the introduction of MRI into the diagnostic PCa-care pathway has increased the accuracy of PCa detection and seems to be able to decrease the invasiveness of the monitoring protocol. The achieved improvements with respect to diagnostic accuracy should off-course be embraced, but at the same time we should start reconsidering our classical definition of significant disease. The aim of AS is to reduce overtreatment of low-risk PCa and the published, pre MRI-era, excellent long-term disease-specific survival of AS-patients informs us that for many patients AS is indeed the best treatment strategy. Without challenging our definitions, we may be taking a step back in the sense that improvements may lead to more harm, while in fact they should expose patients to less harm. Maintaining our inclusion criteria for AS from the systematic biopsy era will unnecessarily and undesirably expose patients to the increased risk of overtreatment. The evidence behind the addition of MRI-targeted biopsies to systematic biopsies calls upon the re-evaluation of the AS inclusion criteria.

7. Future directions

Following the re-evaluation of the AS inclusion criteria, the currently existing AS-protocols should be closely examined too. So far, the existing AS-protocols rely on the notion of one-size-fits-all. But to accommodate the inclusion of the MRI into the AS follow-up protocol, to increase the adherence to the follow-up AS schedules and to decrease the drop-out rate of men on AS without signs of progression, a more dynamic and individual risk-based AS-approach should be investigated further (Fig. 1) [3]. Such an effort in creating risk-based personalized AS biopsy schedules are currently being explored in the Movember Foundation's third Global Action Plan (GAP3) study and in the PRIAS study [35, 36]. Further development and validation studies of the individual risk-based AS approach are, however, warranted before implementation into clinical practice is possible.

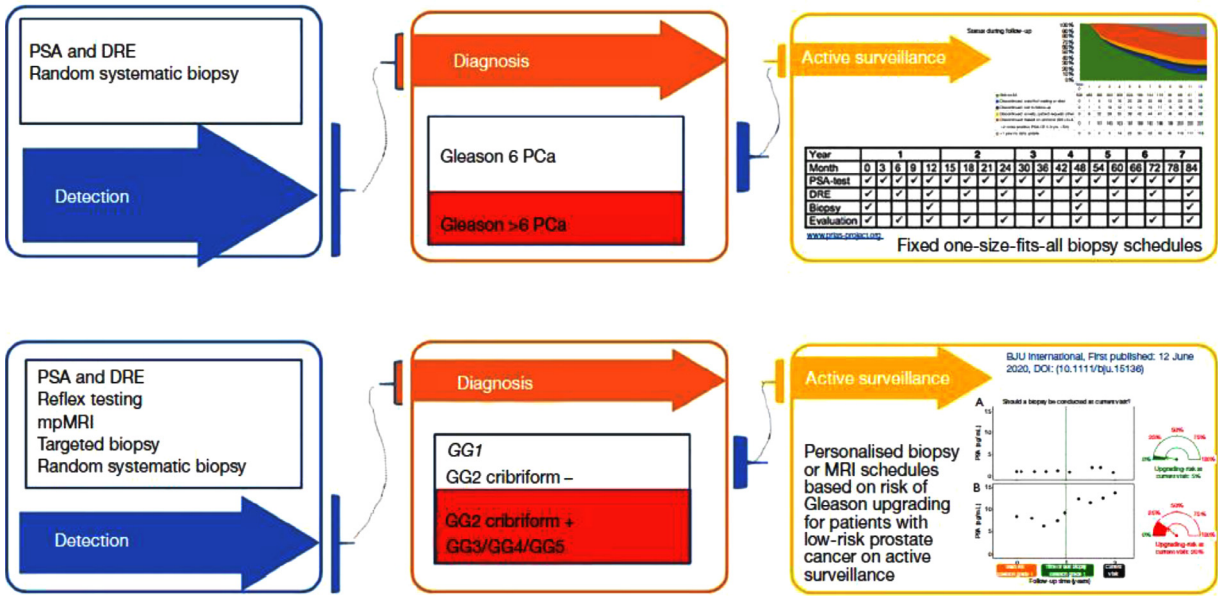

Fig. 1. Identification, detection and active surveillance according to a one-size-fits-all approach (traditional, represented in the upper part of the figure) and an individual dynamic risk-based approach (future, represented in the lower part of the figure) [3].

Conflict of interest

The authors do not have any conflict of interest to disclose.

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