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Platinum Opinion – EAU Guidelines View

Standard Repeat Biopsies During Active Surveillance for Prostate Cancer: Are They Necessary in the Magnetic Resonance Imaging Era?

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1. Active surveillance in the magnetic resonance imaging era

When active surveillance (AS) for prostate cancer (PCa) was introduced as an alternative to active treatment, the diagnostic algorithm consisted of prostate-specific antigen (PSA) measurement and/or digital rectal examination (DRE) followed by sextant systematic biopsies. Several prospective AS studies have shown favourable long-term oncological outcomes using these classic eligibility criteria [1].

Different novel diagnostic tools have become available since then. Risk calculators and magnetic resonance imaging (MRI) have reduced the number of unnecessary biopsies. MRI also altered the biopsy core strategy by allowing targeting of the most abnormal areas. In men who undergo biopsy, this targeted-cores strategy optimises detection but also results in a grade shift [2]. Men with International Society of Urological Pathology grade group (GG) 1 disease on systematic biopsy are now being classified as having a higher GG, while harbouring the exact same tumour previously considered appropriate for AS [3]. This increases the risk of overtreatment, as urologists remain concerned that GG 2 disease with otherwise favourable characteristics is clinically significant on the basis of historical data [4].

2. Standard repeat biopsy

The DETECTIVE study led to consensus that men eligible for AS after combined systematic and MRI-targeted biopsy do not require a confirmatory biopsy [5]. Considering the improved concordance in GG assignment between targeted biopsy and prostatectomy specimens, the indication for standard confirmatory biopsy before starting AS seems limited in comparison to diagnosis based on systematic biopsy.

However, repeat biopsy every 2–3 yr is still recommended, as histopathological assessment is most closely associated with true tumour status and represents the most objective criterion for AS (dis)continuation [6,7]. Therefore, treatment decisions should predominantly be based on histopathological progression rather than on rising PSA levels or even progressive features on imaging [6]. However, real-life data show underutilisation of repeat prostate biopsies in clinical practice [8].

The aim of protocol-directed repeat biopsy during AS is timely detection of pathological progression or compensation for potential previous undersampling, but its value may be variable and results can be difficult to interpret correctly. A standard protocol for repeat biopsy does not consider the differences in risk and resulting "number needed to biopsy" (NNB) to find one additional significant PCa. As a comparison, the EAU guidelines recommend no biopsy in the primary diagnostic setting for groups with a risk of <10% for GG ≥2 cancer (3–8%) [6].

The definition of upgrading has also changed, as the eligibility criteria for AS have expanded in response to the grade shift due to MRI targeted cores, and now also include GG 2 PCa with otherwise favourable characteristics. Therefore, it seems counterintuitive to use GG 2 as a relevant endpoint in AS studies. GG ≥3 may be a more appropriate

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endpoint. The number of previous biopsy sessions may also be considered, as taking more biopsy cores from the prostate will by definition increase the risk of finding higher GG, but concurrently reduces the likeliness that this is a relevant finding because of repeat testing bias. Tumours upgraded during follow-up therefore have more favourable outcomes than tumours with a similar GG detected at initial biopsy, as a higher cumulative number of cores was required before this GG was detected [9].

Finally, the timing of finding higher-risk disease during AS should be considered. A limited delay in detecting significant disease is unlikely to cause additional unfavourable outcomes among men with such initial favourable disease characteristics. Even a delay in definitive surgery of up to >12 mo after upgrading to GG 2 was not associated with recurrent disease [10].

3. MRI changes during AS

It is well accepted that high-quality MRI predicts the presence of clinically significant PCa [2]. Although standard serial MRI is not yet recommended in the EAU guidelines, one could extrapolate that MRI would also allow early detection of an aggressive cancer in men undergoing AS. The frequency of MRI may follow the elected repeat biopsy schedule, which should at least not be less than the minimum 2–3-yr interval used in protocols such as PRIAS, with a higher frequency to be considered in cases with relative risk factors. The higher the threshold for defining upgraded disease, the better the "rule-out" performance of MRI changes during AS. A review by Rajwa et al [11] showed that use of MRI progression as an indication for repeat biopsy resulted in sensitivity of 0.587, specificity of 0.750, a positive predictive value (PPV) of 0.496, and a negative predictive value (NPV) of 0.848 for upgrading (GG 2–5). MRI-based AS would avoid repeat biopsy in up to 68% of patients, while missing 12% of PCa progression cases. Using the more relevant GG 3–5 as the endpoint, the sensitivity, specificity, PPV, and NPV were 0.695, 0.619, 0.134, and 0.954 respectively. The good NPV (considering low prevalence) may be particularly relevant for selected patients with a low risk of upgrading.

The information obtained via MRI during AS may be optimised using standardised PRECISE (Reporting Prostate Magnetic Resonance Imaging in Patients on Active Surveillance for PCa) scores. A consensus statement emphasised the importance of a quality standard for scans, that all previous scans need to be taken into account, that the PRECISE score is the highest score for any lesion, and that lesion visibility is an important factor in a PRECISE score of 3 [12]. Gaps in knowledge on how to measure tumour size and on the definition of a significant size increase were also identified. There was also consensus that changes on repeat MRI during AS should not be used to change management strategy, but rather should trigger a confirmatory biopsy before considering active treatment [13]. It could make sense to use MRI lesion-diameter thresholds or the occurrence of additional lesions confirmed to harbour GG $\geq$2 PCa as surrogates for treatment indication, especially since the percentage of positive systematic biopsy cores is no longer available owing to the altered recommendation on biopsy strategy in the primary diagnostic setting. However, there is no evidence showing that changes in imaging alone should direct active therapy without histopathological evidence of progression.

4. Risk stratification for repeat biopsy

During follow-up, repeat biopsy at least every 2–3 yr is still recommended. Besides novel imaging-based predictors of upgrading, such as changes on MRI, classic baseline variables remain important in predicting the course of the disease. PSA density is one of the strongest predictors and often has predictive value, particularly when used in combination with imaging. Besides PSA density and MRI morphological kinetics, other factors associated with low progression rates include slowly rising PSA and previous negative repeat biopsy. The combination of favourable low PSA density at baseline and stable or regressing disease (PRECISE score of 1–3) on MRI during follow-up therefore identifies a very favourable group [14]. Here, the NNB to find one relevant case may not justify standard repeat biopsy. The EAU guidelines therefore contain a weak recommendation that serial MRI can be used to identify men for whom standard repeat biopsy may be omitted as they have a very low risk of pathological upgrading at standard repeat biopsy (low-risk PCa, stable MRI PRECISE score of 1–3, and a stable and low PSA density of <0.15 ng/ml/cm^3).

5. Future challenges

Additional challenges arise when moving towards a more individualised and imaging-based AS strategy. Quality issues as encountered in the diagnostic setting may be even more relevant for AS follow-up. The frequent repeat MRI scans and comparison with previous scans during follow-up may have an important impact on imaging capacity. Implementation of MRI-based repeat biopsy instead of standard repeat biopsy may therefore differ by country and centre. The definition of significant PCa and the point at which to stop AS, especially given the grade shift caused by MRI-targeted biopsy, have not been fully established. Dynamic surveillance may further optimise prediction of outcomes [15]. Finally, with the lower risk of infectious complications with transperineal biopsy in comparison to a transrectal biopsy approach, the incentive to avoid biopsy may have decreased.

AS remains an important tool in efforts to decrease overtreatment of PCa. Eligibility for AS should be expanded, while minimising the burden of follow-up at the same time, exploiting the possibilities of modern diagnostics. In modern practice, prostate biopsy should be preceded by MRI, and if MRI findings remain unchanged in combination with favourable characteristics such as PSA density, discussion with the patient regarding the relative risks and benefits of repeat biopsy should be considered.

Conflicts of interest: Roderick C.N. van den Bergh is a consultant for Astellas and Amgen; has received speaker honoraria from MSD and Ipsen; has participated in trials for Janssen; and has received research

grants from Astellas and Janssen. Philip Cornford has received honoraria or consultation fees from Accord Healthcare, Bayer UK, Bristol-Myers Squibb, and Janssen Cilag, and speaker honoraria from AstraZeneca and Ipsen Biopharm. Ivo G. Schoots has nothing to disclose.

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