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Indication for Active Surveillance in the Era of MRI-Targeted Prostate Biopsies

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Keywords
Active surveillance · MRI-targeted prostate biopsy · MRI-TRUS fusion prostate biopsy · Prostate cancer · Tumor volume

Abstract
Introduction: Active surveillance (AS) strategies were established to avoid overtreatment of low-risk prostate cancer (PCa) patients. Low tumor volume represents one indication criteria; however, applying this criterion after MRI-targeted prostate biopsies may lead to overestimation of tumor volume; wherefore, patients suitable for AS would be exposed to the risk of overtreatment. ***Methods:*** This retrospective analysis included 318 patients in which PCa was detected by MRI-TRUS fusion prostate biopsy. Classic and extended indication for AS included Gleason 6 and Gleason 3 + 4 cancer, respectively. We assessed the effect of targeted biopsies and temporary rating strategies on eligibility for AS and developed new "composite" algorithms to more accurately assess eligibility for AS. ***Results:*** Forty-four (13.8%) and 60 (18.9%) of the 318 patients qualified for AS according to "classic" and "extended" criteria, respectively. Application of the "composite 1" definition led to AS eligibility of 52 of 248 patients (20.97%) in the classic and of 77 of 248 patients (31.05%) in the "extended" group. ***Conclusions:*** We could demonstrate that classic algorithms led to ineligibility of patients for AS. We propose a new rating algorithm to improve tumor assessment for a more accurate indication for AS.

Introduction

The introduction of prostate cancer (PCa) screening programs has led to a significant increase in the PCa incidence [1] but consequently also to overdetection and overtreatment of clinically insignificant cancers [2]. MRI-targeted biopsy approaches have the potential to overcome these problems [3] by yielding superior accuracy, as demonstrated in the recent PROMIS [4] and PRECISION [5] trials. However, such highly sophisticated biopsy systems are not commonly available, and many low-risk PCa, which have a small chance of progression or ever causing symptoms or death, are still detected and overtreated. In order to avoid overtreatment and treatment-related morbidities, active surveillance (AS) strategies

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have been developed; patients with cancers thought to pose minimal risk to life are not hastily treated but initially only closely monitored, and curative treatment is only recommended if higher risk features are detected during the follow-up. Numerous AS criteria have been suggested [6]. The common criteria comprise low clinical stage (cT1-cT2) based on digital rectal examination and low tumor volume, low Gleason score (GS) (<7; ISUP grade 1), and favorable prostate-specific antigen (PSA) values (<10 ng/mL) and PSA kinetics [7–9]. AS is considered an appropriate strategy for patients with low-risk nonmetastatic PCa [8–10]. Studies like the PRIAS study [11] demonstrated that the compliance with strict eligibility criteria leads to low rates of reclassification or progression during AS. In contrast, the choice of more liberal criteria can result in higher rates of reclassification or progression with subsequent unjustified radical treatment. Among other studies, the ProtecT trial [12] included patients with Gleason 7 disease into AS and demonstrated PCa-specific survival rates of 98% at 10 years. Klotz et al. [13] reported the development of metastases in 9.1% of Gleason 7 patients, with a median time to metastasis of 7.3 years. Other large cohorts including Gleason 7 PCa patients have not reported results stratified for Gleason 7 [14, 15]. The limited available data suggest that AS can be a safe strategy for patients with low volume Gleason 7 (3 + 4) cancer; however, associated with a higher risk of progression or metastasis [12]. Notably, the first guidelines allowing consideration of patients for AS if the Gleason 4 pattern does not exceed 10% were issued by Cancer Care Ontario [10].

So far, the role of MRI diagnostics and MRI tumor volume in risk stratification is yet to be determined [16]. Until today, tumor volume is still reflected by the number of biopsy cores and the percentage of biopsy core involvement. According to the EAU guidelines, AS should only be offered to patients with ≤2 positive biopsy cores and a minimal biopsy core involvement of ≤50% [8].

As the current guidelines recommend multiparametric MRI (mpMRI) imaging of the prostate in biopsy-naive patients and in patients with prior negative biopsy, the number of MRI-targeted biopsies is steadily growing. Especially the combined use of MRI-targeted and TRUS-targeted biopsy techniques produces good results and shows the least risk of underestimating the Gleason grading, which is the strongest predictor of PCa outcome [17, 18].

As a fact, in addition to the standard random biopsies, several targeted biopsies are usually taken from the same suspicious lesion. This might lead to overestimation of the tumor volume, which is derived from the number and percentage of positive biopsy cores in clinical practice. Due to the fact that only patients with more than 2 positive biopsies qualify for AS, the use of targeted biopsy approaches may ultimately lead to patients who are considered ineligible for an AS strategy. The selection criteria for AS have been developed in the era of random biopsies, and it is unclear how targeted biopsies should be rated. Therefore, this study aims to analyze the effect of targeted biopsies on current guidelines for AS and to addresses potential solutions for an appropriate selection of patients undergoing targeted biopsies for AS.

Table 1. Indication for AS according to classic and extended indication

	Random	Targeted	Combined
Classic Gleason (3+3)	44	37	20
Extended Gleason (3+4)	60	52	24

Classic indication for AS comprises cT1/2 and PSA ≤10 ng/mL and Gleason ≤6 and ≤2 positive biopsies and minimal biopsy core involvement (≤50% cancer per biopsy). Extended indication of AS includes Gleason 7a PCa. AS, active surveillance; PCa, prostate cancer.

Materials and Methods

This study was approved by the Local Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz; EKNZ 2017-02170). 318 patients in which PCa was detected by MRI-TRUS fusion prostate biopsy at the Clinics for Urology of the University Hospital Basel (n = 69) and the Cantonal Hospital of Aarau (n = 249) between January 2016 and November 2018 were enrolled in this retrospective study. On a complete case basis, 248 patients were analyzed.

Biopsies at the University Hospital Basel were performed using real-time virtual sonography (Hitachi Medical Systems, Tokyo, Japan). Biopsies at Cantonal Hospital of Aarau were performed using real-time virtual sonography (Hitachi Medical Systems, Tokyo, Japan) and ArtemisTM (Eigen, CA, USA). Indication for biopsy was made according to European guidelines [8]. All patients received random template biopsies and MRI-targeted biopsies of all suspicious lesions detected in mpMRI. Lesions classified as PI-RADS 3–5 according to the PI-RADS 2.0 classification were deemed suspicious [19]. All patients had at least one suspicious PI-RADS lesion. Demographic and clinical data such as age, PSA values, and clinical stage, and detailed information on MRI findings, biopsy, and histologic findings were extracted by chart review.

All patients were screened for eligibility for AS according to current European guidelines [8], in the further course referred to

as "classic" indication (Table 1). We also defined an "extended" indication group that includes patients with favorable intermediate risk PCa Gleason 7 (3 + 4) on top. We wanted to find out how targeted biopsies influence the indication for AS, and which of the criteria (GS upgrading, >2 positive biopsy cores, or biopsy core involvement of >50%) might lead to ineligibility for AS. Furthermore, we compared the eligibility for AS based on the results of random biopsies only, targeted biopsies only, and for all biopsies combined. Moreover, we compared these results with eligibility for AS based on a "composite 1" definition based on PSA, GS in all biopsies, in combination with the number of positive random biopsies and according tumor involvement, and a "composite 2" definition based on PSA, GS in all biopsies, in combination with MRI-measured tumor volume.

Tumor volume was calculated based on the mathematical formula of spheroid volume ($V = 4/3\ \pi\ abc$), with a, b, and c representing the tumor dimensions. Only 2 diameters are given in MRI reports. PCa volume of the largest lesion per patient and the "combined" volume of all lesions per patient were calculated based on the lesions with histologic cancer detection. Tumor volume according to a lesion volume ≤0.5 cm^3 was defined as clinically not significant [20]. Instead of using the number of positive random biopsies and according tumor involvement to estimate tumor extent, we used MRI-measured tumor extend in the composite 2 definition.

All statistical inference testing and data visualization were performed using R 3.5.2. All correlations were performed using the Spearman method. If necessary, variables were log-transformed. All tests were performed at a significance level of $\alpha = 0.05$. We implemented a simple linear regression model in order to predict a significant tumor volume as a cutoff, as shown in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517300. Additional parameters, such as PSA, were assessed regarding their additional predictive power but were excluded due to nonsignificant contributions to the model performance.

Results

Descriptive patient characteristics are summarized in Table 2. According to classic indication, 44 patients qualified for AS based on the results of random biopsies only, 37 patients qualified based on the results of targeted biopsies only, and 20 patients based on all biopsies combined (Table 1). According to extended indication including favorable intermediate risk PCa, 60 patients qualified for AS based on the results of random biopsies only, 52 patients based on the results of targeted biopsies only, and 24 patients based on all biopsies combined (Table 1).

Considering all biopsies led to ineligibility of 24 patients (54.5%) in the classic indication group and to ineligibility of 36 patients (60%) in the extended indication group. The reasons for dropout in the classic and extended indication groups were upstaging of the GS in 9 and 5 patients, the number of positive biopsies (>2) in 11 and 19 patients, and core involvement of >50% in 5 and 6 patients, respectively (Table 3). Multiple reasons for dropout applied in 6 and 8 patients, respectively (Table 3).

Table 2. Baseline characteristics

Age at biopsy, years, median (IQR)	67 (62–72)
Prostate volume TRUS, mL, median (IQR)	43.5 (33–59)
Prostate volume MRI, mL, median (IQR)	42.42 (29–54)
PSA, ng/mL, median (IQR)	6.3 (4.7–9.6)
PSA density, ng/mL/mL, median (IQR)	0.15 (0.1–0.23)
Days from mpMRI to biopsy, median (IQR)	32 (20–48)
Maximum lesion dimension, mm, median (IQR)	12 (7–22)
Biopsies (random) per patient, median (IQR)	13 (12-16)
Biopsies (targeted) per patient, median (IQR)	7 (4–9)
Biopsies (total) per patient, median (IQR)	21 (19–24)
Digital rectal examination, *n* (%)	
Unknown	6 (1.9)
Bilateral	13 (4.2)
Left	19 (6.1)
Right	25 (8)
No suspicion	249 (79.8)
Family history of PCa, *n* (%)	
Yes	22 (7.1)
No	62 (19.9)
Unknown	228 (73.1)
Total number of lesions per patient, *n* (%)	
5 lesions	3 (1)
4 lesions	19 (6.1)
3 lesions	45 (14.4)
2 lesions	128 (41)
1 lesion	110 (35.3)
PIRADS, *n* (%)	
PIRADS 3	170 (29.6)
PIRADS 4	297 (51.7)
PIRADS 5	108 (18.8)

PSA, prostate-specific antigen; mpMRI, multiparametric MRI; PCa, prostate cancer.

Table 3. Reasons for ineligibility for AS in the classic and extended indication group

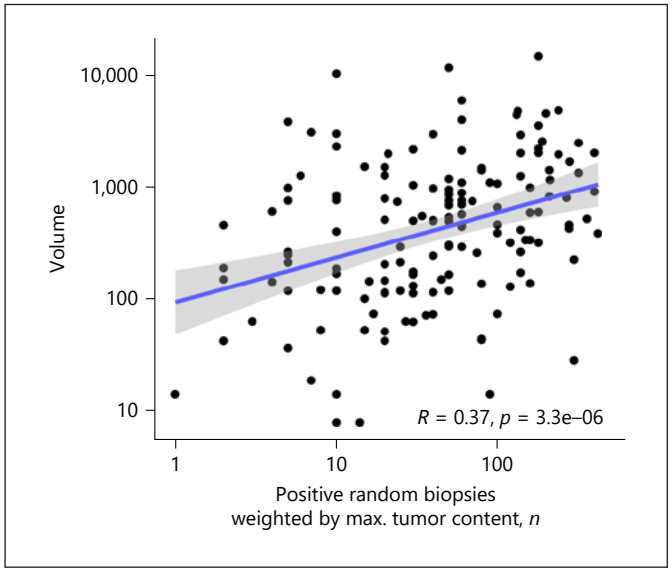
	Classic Gleason (3+3)	Extended Gleason (3+4)
GS	9	5
>2 positive biopsies	24	35
>50% tumor content in any biopsy	5	8
Multiple reasons		
2 reasons	6	8
3 reasons	4	2

GS, Gleason score; AS, active surveillance.

Table 4. Eligibility for AS according to composite 1 definition in the classic and extended indication group

	Composite 1		
	not qualified, % (*n*)	qualified, % (*n*)	total, % (*n*)
Classic			
Not qualified	75.40 (187)	6.85 (17)	82.26 (204)
Qualified	3.63 (9)	14.11 (35)	17.74 (44)
Total	79.03 (196)	20.97 (52)	100 (248)
Extended			
Not qualified	66.94 (166)	8.87 (22)	75.81 (188)
Qualified	2.02 (5)	22.18 (55)	24.19 (60)
Total	68.95 (171)	31.05 (77)	100 (248)

AS, active surveillance.



Color version available online

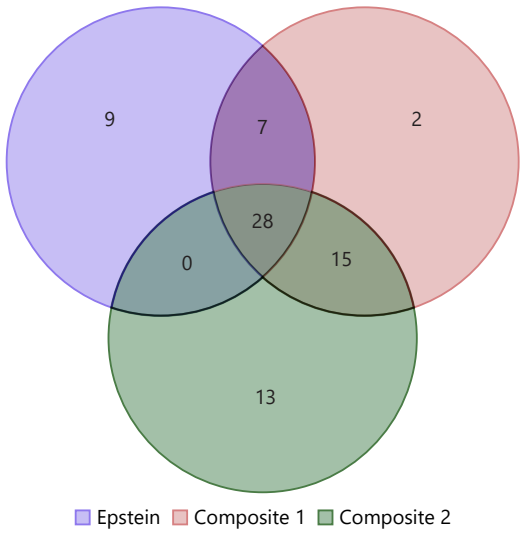
Fig. 1. Correlation of biopsies with MRI tumor volume.

The application of composite 1 definition led to eligibility of 52 of the 248 patients (20.97%) in the classic group (Gleason 6) and to 77 of the 248 patients (31.05%) in the extended group including favorable intermediate risk PCa (Table 4). Application of composite 2 definition led to eligibility of 41 of the 157 patients (26.11%) in the classic group (Gleason 6) (Table 4).

The number of positive random biopsies significantly correlated ($R = 0.29$, $p < 0.01$) with the respective largest tumor volume (data not shown). Surprisingly, the fraction of positive random biopsies (number of positive random biopsies divided by the total number of random biopsies) showed a weaker, albeit still significant, correlation ($R = 0.17$, $p = 0.04$) with the respective largest tumor volume (data not shown).

The number of positive random biopsies significantly correlated ($R = 0.34$, $p < 0.01$) with the calculated tumor volume combining all lesions per patient (data not shown). Again, the fraction of positive random biopsies showed a weaker, but still significant, correlation ($R = 0.18$, $p = 0.02$) with the calculated tumor volume combining all lesions per patient. The combination of fraction of positive random biopsies with maximum core involvement significantly correlated ($R = 0.29$, $p < 0.01$) with the calculated tumor volume combining all lesions per patient (data not shown).

The number of positive random biopsies in combination with maximum core involvement significantly correlated ($R = 0.37$, $p < 0.01$) with the calculated tumor volume combining all lesions per patient (Fig. 1). We therefore fitted a linear model to predict the MRI volume that corresponds to 2 positive random biopsies and with maximum 50% tumor content (online suppl. Table 2). This yielded a predicted volume of 0.52 cm^3, which is close to the previously proposed cutoff for significant tumor volume [20]. We then constructed a new indication algorithm based on the previously defined composite 1 definition with MRI volume replacing the number of random biopsies and tumor content (composite 2). This led to an eligibility of 56 patients (22.5%) for AS. A comparison of patients qualifying for AS according to classic, composite 1, and composite 2 is depicted in Figure 2. Information on MRI volume by indication group is given in online suppl. Table 2.



Volume in cm^3	Gleason score in random biopsies	Gleason score in targeted biopsies
0.1	3 + 3	3 + 4
0.7	3 + 3	3 + 5
2.3	3 + 3	3 + 4
0.7	3 + 3	3 + 4
0	3 + 3	3 + 4
0	3 + 3	3 + 4
0.7	3 + 3	3 + 4
0.2	3 + 3	3 + 4
0	3 + 3	4 + 4
0.7	3 + 3	No tumor
1.3	3 + 3	3 + 3
3.0	3 + 3	3 + 3
1.0	3 + 3	3 + 3
0.8	3 + 3	3 + 3
3.1	3 + 3	3 + 3
1.3	3 + 3	No tumor
0.9	No tumor	3 + 3
1.1	No tumor	3 + 3

Fig. 2. Venn diagram.

Discussion

The concept of AS has first been introduced in 1990 [21] and has been constantly developed over the last decades. Since the first report of application of this strategy [22], it has successfully been used to mitigate overtreatment associated with PSA screening programs. Yet, the eligibility criteria established in this era remained mainly unchanged [7, 23]. Nowadays, mpMRI of the prostate and MRI-targeted biopsies yield significantly improved diagnostic accuracy. Some authors have assessed the impact of the number of targeted biopsy on cancer detection, although the number of targeted biopsies varies significantly [24–26] and no standard has been defined. However, this represents the crux of targeted biopsies; these findings may not be representative for the overall tumor burden and may ultimately lead to overestimation of tumor volume. The PRIAS criteria have been updated to overcome this problem by not limiting the number of positive cores and the percentage of cancer present in the cores.

In our cohort, targeted biopsies led to ineligibility for AS in 24 of 44 (54.5%) and 36 of 60 patients (60%) according to classic and extended indications, respectively (Table 1). The most common reason for ineligibility for AS was the number of positive biopsy cores exceeding 2 (Table 3). However, MRI-measured tumor volume was <0.52 cm^3 in 4 of 11 and 11 of 20 dropouts (due to tumor volume) according to classic and extended indication, respectively. This reflects how the noncritical rating of targeted biopsies can lead to overestimation of the actual tumor burden and at the same time raises the question of whether the assessment of tumor volume based on positive biopsy cores in combination with core involvement is still up-to-date in the era of mpMRI. Furthermore, a valuable conservative treatment option is withheld from these patients.

We therefore evaluated which pathological parameters correlate best with the MRI-measured tumor volume and might thus function as surrogate parameter for tumor volume. We could demonstrate that the

number of positive random biopsies in combination with maximum core involvement significantly correlated with the actual tumor volume (Fig. 1). We calculated the eligibility for AS according to the composite 1 definition, which used the number of random and targeted biopsies, in combination with according tumor involvement as surrogate parameter for tumor volume. Even though this approach is feasible, it also revealed a clinically bothersome variation (Fig. 1; Table 4). Therefore, we assessed the usability of MRI-measured tumor volume as a marker in the composite 2 definition for the eligibility for AS in the classic indication group. The comparison of patients qualifying for AS according to classic, composite 1, and composite 2, as illustrated in Figure 2, highlights the potential advantages of the newer indication algorithms as they take into account the GS from all biopsies and at the same time avoid overestimation of tumor volume resulting from targeted biopsies (see online suppl. Table 1 for full specifications of the indication groups).

Furthermore, our results demonstrate that both application of classic rating strategies and the proposed composite 1 score tend to underestimate tumor volume (Table 5) and enable eligibility for AS in a more liberal fashion as tumor volume exceeded 0.5 cm^3 in a significant number of patients. However, classic rating strategies including targeted biopsies can at the same time lead to overestimation of tumor volume. Due to this dilemma, we encourage the use of a composite 2 definition as this approach yields the advantage of incorporating both GS and MRI tumor volume.

To the best of our knowledge, no other study has assessed composite rating strategies in the context of AS [27, 28]. In addition to the retrospective nature of the study, the relatively small sample size of the cohort represents the main limitation of our study, and our findings should be validated in larger cohorts. Nevertheless, these results are of potential importance for clinicians facing the problem that patients formally do not qualify for AS due to exceeding the maximum number of positive biopsy cores as a result of targeted biopsies. In this situation, the assessment of the actual tumor volume can be helpful for evaluating whether or not AS represents a feasible treatment option for the patient. Furthermore, the composite 2 score represents an up-to-date algorithm that accommodates for the findings of targeted biopsies and tumor volume and can support the clinical decision-making toward AS.

Conclusion

Classic rating strategies for AS tend to underestimate tumor volume. The use of MRI-targeted biopsies requires the verification of temporary indication criteria for AS and the development of new ones. We propose a new rating algorithm to improve tumor assessment for a more accurate indication for AS. These findings are potentially important to improve patient counseling and compliance for conservative treatment strategies.

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Statement of Ethics

The study protocol was approved by the Local Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz; EKNZ 2017-02170).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

C.W., J.F., and M.K.: conceptualization. C.W., J.F., R.M., J.E., and M.K.: investigation. C.W., J.F., R.M., S.W, F.R., H.S., and M.K.: analyzed the data. C.W., J.F., R.M., J.E., C.R., L.M., H.S., S.W., F.R., and M.K.: wrote the manuscript.

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