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INVITED OPINION

Prostate Cancer

Active surveillance for prostate cancer: when to recommend delayed intervention

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There are no agreed upon guidelines for placing patients on active surveillance (AS). Therefore, there are no absolute criteria for taking patients off AS and when to recommend treatment. The criteria used to define progression are currently based on prostate specific antigen (PSA) kinetics, biopsy reclassification, and change in clinical stage. Multiple studies have evaluated predictors of progression such as PSA, PSA density (PSAD), prostate volume, core positivity, and visible lesion on multiparametric magnetic resonance imaging (mpMRI). Furthermore, published nomograms designed to predict indolent prostate cancer do not perform well when used to predict progression. Newer biomarkers have also not performed well to predict progression. These findings highlight that clinical and pathologic variables are not enough to identify patients that will progress while on AS. In the future, with the use of imaging, biomarkers, and gene expression assays, we should be better equipped to diagnose/stage prostate cancer and to distinguish between insignificant and significant disease.

WHEN TO RECOMMEND TREATMENT AFTER INITIAL SURVEILLANCE

There is no consensus or agreed upon guidelines for placing patients on AS. Therefore, there are no absolute criteria for taking patients off AS and when to recommend treatment. Each institution has its own protocol for AS that is based on PSA and biopsy information. When patients demonstrate progression from these initial parameters, patients are offered definitive local treatment with curative intent. Also, there is no standard definition of progression. The relevant question: is progression really progression or shortcomings in our ability to clinically diagnose/stage prostate cancer?

CRITERIA FOR PROGRESSION

The criteria used to define progression are currently based on PSA kinetics, biopsy reclassification, and change in clinical stage. PSA kinetics is used as PSA doubling time (PSADT) or PSA velocity. Biopsy reclassification consists of a change in Gleason score ≥7 and/or an increase in the volume of cancer. An increase in the volume of cancer can be an increase in the number of positives cores and/or an increase in the amount of cancer in any given positive biopsy core. **Table 1** lists the progression criteria for the published AS cohorts.[1]

PREDICTORS OF PROGRESSION

From the AS cohorts, we know that one-third of AS patients will progress, and most will do so within the first 2–3 years. Multiple studies have evaluated clinical and pathologic variables as well as mpMRI to predict disease progression. A negative confirmatory biopsy is associated with a lower likelihood of progression,[2–5] and the risk continues to decrease with each subsequent negative biopsy. In the McGill AS cohort, Barayan *et al*. found that only PSAD >0.15 was an independent predictor of progression,[3] and Kotb *et al*. found that the risk of tumor upgrading was 10% and 31% for PSAD ≤0.15 and >0.15, respectively.[6] Other predictors of progression include percentage free/total PSA and percentage core involvement >35%,[5] African American race, 2 positive cores, and lower prostate volume.[4] The prostate research international AS (PRIAS) protocol found that age, baseline PSA, PSAD, PSADT <3 years, and 2 positive biopsy cores were associated with reclassification at repeat biopsy.[7] In a retrospective study of 298 patients qualified for AS according to the PRIAS criteria, a visible lesion on mpMRI was associated with unfavorable disease at RP in multivariate analysis.[8]

PREDICTIVE NOMOGRAMS FOR INDOLENT DISEASE

Four groups have published nomograms for identifying patients with indolent prostate cancer. When using these nomograms to determine which patients develop biopsy progression or any progression (biopsy and/or surgical progression) within the UCSF AS cohort, the nomogram performances were modest at best with area under the receiver operator curves (AUC) ranging from 0.52 to 0.70.[9] Decision curve analysis showed that the nomograms increased net benefit of treatment only when the threshold probability of biopsy progression or any progression was between 40% and 60%.[9] This suggests most of the net benefit was realized for men with intermediate risk of progression. In this study, none of the nomograms showed any net benefit for the prediction of surgical progression in the subgroup of patients who underwent radical prostatectomy. This analysis highlights that clinical and pathologic variables are not enough to identify patients that will progress while on AS.

BIOMARKERS

van As *et al*. evaluated 326 men on AS and found that percent free PSA was a significant predictor to radical treatment at 2 years, with an AUC of 0.81. Patients with both favorable PSA (<6.4 ng ml^{-1}) and percent free

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Table 1: Criteria for progression among different active surveillance cohorts. Reproduced with permission from Thomsen *et al.*[1]

Publication	*Gleason score*	*Positive cores*	*Percentage cancer involvement per single core*	*Percentage positive biopsy cores*	*PSADT (years)*	*PSAV (ng ml^{-1} per year)*	*cT stage*
Dall'Era *et al.*[17]	Increase					>0.75	
Ercole *et al.*[18]	Progression	Increase	Increase				Change
Klotz *et al.*[19]	≥4+3				<3		Increase cT
Soloway *et al.*[20]	Grade>3	>2					
Tosoian *et al.*[21]	>6	>2	>50				
Ischia *et al.*[22]	Upgrade						Upstage
Bul *et al.*[7]							
Godtman *et al.*[23]	Upgrade						Upstage
Thomsen *et al.*[24]	≥3+4	>3			<3/5*		Increase cT
Selvadurai *et al.*[25]	≥4+3			>50		>1	

*Curative treatment was recommended for patients with PSADT <3 years and treatment options were discussed with patients with a PSADT between 3 and 5 years. PSADT: prostate specific antigen doubling time; PSAV: prostate specific antigen doubling velocity

PSA (≥18%), one favorable, or both favorable had histologic progression rates of 0%, 28%, and 35%, respectively.[10]

In one study of 167 men in the Johns Hopkins AS program, 63 (38%) progressed according to the Epstein criteria, and lower percent free PSA and higher prostate health index were associated with biopsy reclassification and Gleason score upgrading.[11] In another study of 294 men undergoing AS, the PCA3 scores of men who had stable disease and who progressed were not significantly different. Furthermore, the AUC for PCA3 to predict the biopsy progression was only 0.59.[12]

Within the Canary Foundation Prostate Active Surveillance Study of 387 men, median values of PCA3 and TMPRSS2:ERG increased with both increasing number of positive cores and Gleason score. However, AUC for both biomarkers combined to predict Gleason 7 disease (0.66) was smaller than that of PSA alone (0.68).[13]

ERG protein expression was evaluated for risk of progression in a cohort of 265 men undergoing AS, and ERG positivity proved to be a significant predictor of progression in Cox regression analysis (hazard ratio 2.45, $P < 0.0001$). The incidence of progression at 2 years for ERG positive and negative men was 21.7% and 58.6%, respectively.[14]

IMAGING

Multiparametric MRI may be helpful in identifying patients who progress while on AS and who should undergo treatment. In a study by Stamatakis *et al*., a retrospective review was performed of 85 patients who qualified for AS according to the Epstein criteria and who underwent mpMRI.[15] A nomogram was developed using only imaging characteristics, including number of lesions, highest MRI suspicion (low, medium, or high), and total lesion volume to total prostate volume.[15] The nomogram performed best as a diagnostic test to determine which patients should remain on AS since it had a good negative predictive value. Morgan *et al*. described how a prostate lesion can change over time in apparent diffusion coefficients (ADCs) derived from diffusion-weighted MRI.[16] In patients that progressed while on AS, there was a significant reduction in ADCs at follow-up compared to nonprogressors. The authors reported that a 10% reduction in tumor ADC had a 93% sensitivity and 40% specificity in identifying progressors.[16]

CONCLUSIONS

There is no standard definition of progression or established guideline for urologists to follow regarding when to recommend definitive local therapy after initial AS. Current practice is to recommend treatment when there is a deviation in clinical and pathologic parameters such as a change in PSA kinetics, biopsy reclassification, and upstaging from original diagnosis. This opinion piece demonstrates that clinical and pathologic information from the prostate biopsy alone are not good enough to predict progression. mpMRI can help better select patients for AS if a targetable lesion is identified. In the future, biomarkers and gene expression profiling of prostate biopsy tissue will help us to more accurately identify which patients have low-risk disease and can be safely placed on surveillance with a low risk of progression. However, biomarkers need to be validated in larger prospective cohorts of men undergoing AS. Gene expression assays such as Prolaris and Oncotype DX can help risk stratify patients considering surveillance, as well as help tailor follow-up protocols. Prolaris is a 46-gene expression signature that measures RNA expression levels of cell cycle progression genes, and Oncotype DX is a 17-gene panel that evaluates the expression of genes involved in four biological pathways including androgen signaling, cellular organization, stromal response, and proliferation. In the future, with the use of mpMRI, biomarkers, and gene expression assays, we will be better equipped to diagnose/stage prostate cancer and to distinguish between insignificant and significant disease.

COMPETING INTEREST

No competing interests to disclosure.

EDITORIAL COMMENT—(BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

As discussed in many forums, the essential three elements of AS for prostate cancer include: (1) criteria for inclusion, (2) monitoring techniques, and (3) rules for recommending delayed intervention. Dr. Babaian reviews the later topic and discusses several emerging criteria that are developing, despite a lack of uniformity in all three elements. An interesting question to pose for this topic is whether or not delayed intervention really represents a failure of AS. For the purposes of refining AS along the goal of initially classifying patients who will never progress to therapy versus those who will, then delayed intervention can be viewed as a surrogate "failure" endpoint. Yet many patients approach AS differently and would like to delay side effects of treatment, even if not for long periods of time. If the delay of side effects is the goal, then perhaps much longer-term endpoints will need evaluation such as developing metastatic disease risk. Therefore, in evaluating predictors of delayed intervention, we will have to separately look at treatment triggered by mild increases in low-grade tumor volume or upgrading to Gleason 3 + 4, and try to specifically predict

high-grade tumor. As Dr. Babaian points out, genomics and imaging give added dimensions to this challenge. The article updates our current situation, but the rules for AS seem to be changing at a rapid pace.

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