DIFFERENCE OF OPINION

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Super active surveillance for low-risk prostate cancer | *Opinion: No*

Saum Ghodoussipour [1], Amir H. Lebastchi [2], Jonathan B. Bloom [2], Peter A. Pinto [2], Andre Berger [1]

[1] USC Institute of Urology and Catherine & Joseph Aresty Department of Urology, University of Southern California, Los Angeles, CA, USA; [2] Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

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INTRODUCTION

Prostate cancer (PCa) is diagnosed in over 170,000 men in the United States each year (1). While this makes PCa one of the most common solid malignancies in men, the mortality is low and most men die from unrelated causes (1). In fact, almost half of men with screening detected and localized PCa are considered candidates for deferred treatment or active surveillance (AS) (2). To decrease the morbidity associated with definitive therapy, many providers recommend AS for those with very-low (VLR), low risk (LR) disease and in selected favorable, intermediate risk (IR) PCa (3-5).

The use of AS has been steadily increasing and is supported by large cohort studies showing 98-100% PCa specific survival rates (6, 7). While the recommended follow-up for AS varies, safety is predicated on close surveillance with predefined thresholds for treatment based on identification of cancer progression yet still curable disease. In the largest published AS cohort of 993 men with median follow-up of 6.4 years, 10-year cancer specific survival (CSS) was 98.1%. However, 27% of these patients ultimately underwent surgery for indications ranging from prostate specific antigen (PSA) progression, biopsy Gleason score progression or patient preference. While this cohort included mostly younger men with LR disease (Age <70, cT1/T2a disease, PSA <10ng/ml), they also included patients older than 70 with Gleason 3+4=7 or lower disease, such that 20% had IR (6). A separate analysis of this cohort by Musunuru et al. showed that while only 3% of patients developed metastases, metastasis free survival (MFS) was significantly lower in the IR as compared to the LR group (84% vs 95%, p=0.001) (8). Another separate cohort analysis by Yamamoto et al. showed a significantly higher risk of 15-year PCa mortality (PCM) for higher Gleason score disease (HR of 4.0 for Gleason 3+4=7 vs Gleason 3+3=6 and HR 10.5 for Gleason 4+3=7 vs Gleason 3+3=6) (9). The PROTECT trial randomized 1643 patients with localized PCa into AS (n=545), definitive treatment with radical prostatectomy (RP; n=553) or radiation therapy (RT; n=545). There was no difference in PCM amongst the 3 groups (p=0.48), however, of those 17 patients who passed away, 8 were in the AS group (5/8 with IR disease), 5 in the RP group and 4 in the RT group. The rate of disease progression and development of metastases was significantly higher in the AS group as compared to RP or RT (112 vs 46 vs 46 men, respectively; p<0.001) (10).

Despite a certain subset of patients who seem to do worse on AS, concerns with morbidity from definitive treatment have led experts to recommend a broadening of the indications for AS and to include selected patients with low volume IR disease (3, 5, 11, 12). As the indications for AS expand, certain patients may wish to be even more "active" in their surveillance. In 2018, Bloom et

al. proposed the concept of "*Super-Active Surveillance*" (*SAS*), which they defined as focal therapy of an index lesion in order to alleviate concerns of disease progression or ultimate need for definitive treatment (13). While studies have shown the feasibility of ablative techniques, the use of *SAS* remains a work-in progress with controversy regarding the ideal candidate, appropriate follow-up and triggers for more definitive treatment. As it stands, *SAS* should only be performed in the hands of well-experienced providers, ideally as part of an investigational study. Herein, we explore the rationale behind SAS and address the lingering but significant questions that require answering before adoption of this as a mainstream approach.

Multiparametric MRI and the changing paradigm in prostate cancer diagnosis

The diagnosis of PCa has classically been via systematic ultrasound guided biopsy. However, this method under stages 30% of men with PCa (14-18). This is thought to be due to under sampling or poor visualization of hard to reach areas such as the apex or anterior zones. Multiparametric magnetic resonance imaging (mpMRI) has emerged as an important diagnostic tool in PCa as it allows more accurate sampling of the prostate so that clinicians will identify more clinically meaningful PCa while avoiding overtreatment of clinically insignificant disease (19, 20). The enhanced ability of mpMRI to detect significant disease comes from mpMRI guided biopsy techniques where suspicious lesions (not visible on US) are targeted during the biopsy (21, 22). The use of mpMRI is now recommended by guideline panels in patients considering AS but with suspicion of significant cancers (3-5).

While mpMRI-guided targeted biopsy is now the preferred approach, some have even proposed an extended role for mpMRI as a replacement for biopsies in those patients on AS (23-26), especially as this image modality has also demonstrated superior detection of progression compared to other markers such as PSA and digital rectal exam (26). However, data supporting the practice of mpMRI as a replacement for repeat biopsy come from single centers that are well experienced with the use of this image modality. Interpretation should come with caution especially as mpMRI may miss up to 15% of clinically significant tumors. The reading of mpMRI requires specially trained genitourinary radiologists and academic centers with more experience are better equipped for standardization of care and subsequent biopsies or treatment (27). Margel et al. found an 83% positive predictive value and 81% negative predictive value for mpMRI in reclassifying patients who no longer met criteria for AS (23). A recent study by Panebianco et al., included 1,255 men with negative mpMRI who were treated at a tertiary referral center. A prior negative biopsy had been performed in 596 men and 659 were biopsy naïve. These men were followed for a minimum of 2 years and freedom from any PCa was 94% overall. At 4 years, the freedom from any grade prostate cancer was 84% for those who were biopsy naïve and 96% in those with a prior negative biopsy (28).

Thus, mpMRI clearly improves detection of prostate cancer, but systematic random biopsies are still needed to prevent a missed cancer diagnosis in those at risk but with negative mpMRI (29). Certainly, larger prospective multi--institutional studies are needed in those with negative imaging. In those with positive imaging however, mpMRI guided, targeted biopsy not only improves detection but also may serve as a useful guide for minimally invasive image--guided treatment (13).

Focal ablation: feasible but safe?

The acceptance of image-guided diagnosis in PCa has spawned the era of image--guided treatment, also known as focal therapy. Focal therapy is defined as the specific targeting and ablation of the malignant target of the prostate while leaving benign tissues intact. Methods of ablation vary and include cryotherapy, high intensity focused ultrasound (HIFU), radiofrequency ablation, laser ablation, irreversible electroporation, microwave ablation, photodynamic therapy and water vapor therapy (30). Feasibility of each treatment has been shown, but level one evidence is lacking as studies consist mostly of single center cohorts without long-term follow-up (13).

Focal therapy is based on the hypothesis that an index lesion, drives cancer related outcomes (31-34). However, PCa is known to be a multifocal disease with unilateral disease occurring in only 20-30% of cases (33-35). Just as negative mpMRI may miss disease, focal therapy has the potential to miss cancer and risk progression. Before focal therapy or SAS can be considered a safe option for patients, the ideal candidate, follow-up and definition of treatment failure must be defined.

The ideal patient for focal therapy is still debated without consensus or long-term data. Gill et al. demonstrated the safety of focal therapy in men with LR PCa (as defined by Gleason score 3+3=6, cT2a, PSA ≤10). They compared AS or focal therapy with targeted photodynamic therapy in 413 men and found a lower conversion to radical therapy in the ablation group compared to the AS group (24% vs 53% at 4 years, HR 0.31, 95% CI 0.21-0.45). Cancer progression rates were also lower in the ablation group (HR 0.42, 95% CI 0.29-0.59) (36). The European Association of Urology has put forth a position statement on focal therapy acknowledging that men with low-risk disease are good candidates as most reports have included men with Gleason 3+3=6 disease. However, those with IR risk disease (Gleason ≤4+3) may be considered for focal therapy just as they are considered for AS (37).

Gland and tumor specific variables must be considered as well. For example, the ideal gland size for HIFU is 40 gram and must be without calcifications that may interrupt ultrasound wave transmission (38). Truesdale et al. evaluated patient selection criteria for unilateral cryoablation and they found that pre-treatment PSA, Gleason score, number of cores positive and total tumor length were associated with biochemical and pathologic disease progression (39).

The appropriate follow up for those on SAS must be defined such that treatment failure requiring conversion to more radical therapies can be reliably predicted. Biochemical recurrence (BCR) is a primary endpoint in predicting treatment failure after RP or RT, but no universal criteria for BCR exist after focal therapy of the prostate. While residual disease may exist after focal therapy and potentially can lead to progression, PSA has not been shown to be a good predictor of this risk (40). Viable and benign prostate tissue will continue to produce PSA. Moreover, PSA kinetics in a partially ablated gland differ from those following whole gland ablation, RP or RT (41). The results of repeat biopsy due to PSA based changes are highly variable as studies have found residual disease in 8-45% of cases (39, 42, 43). Routine biopsy performed one year after ablation similarly shows variable rates of residual disease with disease in 0-26% of cases (40, 41, 44, 45). Some have proposed a mpMRI based method of detecting recurrent disease after focal therapy (46) but an inability to define true treatment failure remains: is it any residual disease within the prostate, any clinically significant disease or only clinically significant disease within the ablation zone? Certainly, stronger evidence is needed at this time.

The decision to discontinue AS and proceed to more aggressive treatments currently depends on deterioration of inclusion criteria and not just worsening of mpMRI features or development of new lesions on their own (5). Given the considerable uncertainties in follow--up after focal therapy and outcomes of surgery or radiation after failed ablation, the EAU recommends that patients should be treated with focal therapy only within the context of a clinical trial using predefined criteria (37).

CONCLUSIONS

Paradigm shifts are underway in the management of prostate cancer. AS is a safe and recommended option for patients with LR disease and a favorable risk IR disease. Concerns over disease progression and eventual need for definitive treatment have driven patient interest in alternative options to AS that still avoid the morbidity or surgery of radiation.

The use of mpMRI and fusion biopsy has greatly enhanced urologists' ability to diagnose prostate cancer and to determine patients' candidacy for AS. While focal therapy of these lesions is technically feasible, we are in need of larger, prospective studies with adequate follow up in order to determine true oncologic outcomes. Significant questions remain regarding the appropriate candidate for SAS, follow up as well as triggers for conversion to more definite therapy.

While patient driven excitement may influence urologists to pursue SAS, its use should be reserved for high volume centers with a dedicated focal therapy team under a cautious surveillance protocol. While an exciting option for consideration, SAS should be considered as an investigational option at this time.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Andre Berger, MD
USC Institute of Urology
Keck School of Medicine,
University of Southern California
1441 Eastlake Ave, Suite 7416,
Los Angeles, California 90089.
Fax: +1 323 865-0120,
E-mail: andrekberger@hotmail.com

ARTICLE INFO

Saum Ghodoussipour
https://orcid.org/0000-0001-8901-0210

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