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

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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 Musumuru 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 $\leq 10$). 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 $\leq 4+3$) 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). Trueedale 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.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.
2. Albertsen PC. Observational studies and the natural history of screen-detected prostate cancer. Curr Opin Urol. 2015;25:232-7.
1. National Comprehensive Cancer Network. Prostate Cancer (Version 1.2019). Available from: <https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf>.

4. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options. J Urol. 2018;199:990-7.

5. Briganti A, Fossati N, Catto JWF, Cornford P, Montorsi F, Mottet N, et al. Active Surveillance for Low-risk Prostate Cancer: The European Association of Urology Position in 2018. Eur Urol. 2018;74:357-68.

6. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33:272-7.

7. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. J Clin Oncol. 2015;33:3379-85.

8. Musunuru HB, Yamamoto T, Klotz L, Ghanem G, Mamedov A, Sethukavalan P, et al. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. J Urol. 2016;196:1651-8.

9. Yamamoto T, Musunuru HB, Vesprini D, Zhang L, Ghanem G, Loblaw A, et al. Metastatic Prostate Cancer in Men Initially Treated with Active Surveillance. J Urol. 2016;195:1409-14.

10. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375:1415-24.

11. Dall’Era MA, Klotz L. Active surveillance for intermediate-risk prostate cancer. Prostate Cancer Prostatic Dis. 2017;20:1-6.

12. Cooperberg MR, Cowan JE, Hilton JF, Reese AC, Zaid HB, Porten SP, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol. 2011;29:228-34.

13. Bloom JB, Gold SA, Hale GR, Rayn KN, Sabarwal VK, Bakhutashvili I, et al. “Super-active surveillance”: MRI ultrasound fusion biopsy and ablation for less invasive management of prostate cancer. Gland Surg. 2018;7:166-87.

14. San Francisco IF, DeWolf WC, Rosen S, Upton M, Olumi AF. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. J Urol. 2003;169:136-40.

15. Quintana L, Ward A, Gerrin SJ, Genega EM, Rosen S, Sanda MG, et al. Gleason Misclassification Rate Is Independent of Number of Biopsy Cores in Systematic Biopsy. Urology. 2016;91:143-9.

16. Bul M, Zhu X, Rannikko AS, Staereman F, Valdagni R, Pickles T, et al. Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. Eur Urol. 2012;62:195-200.

17. Taira AV, Merrick GS, Galbreath RW, Andreini H, Taubenslag W, Curtis R, et al. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. Prostate Cancer Prostatic Dis. 2010;13:71-7.

18. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR-ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015;313:390-7.

19. Turkbey B, Mani H, Shah V, Rastinehad AR, Bernardo M, Pohida T, et al. Multimetric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol. 2011;186:1818-24.

20. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378:1767-77.

21. Sonn GA, Margolis DJ, Marks LS. Target detection: magnetic resonance imaging-ultrasound fusion-guided prostate biopsy. Urol Oncol. 2014;32:903-11.

22. Wysock JS, Rosenkranz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol. 2014;66:343-51.

23. Margel D, Yap SA, Lawrentschuk N, Klotz L, Haider M, Hersey K, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. J Urol. 2012;187:1247-52.

24. Nasiari N, Margolis DJ, Natarajan S, Sharma DS, Huang J, Dorey FJ, et al. Targeted Biopsy to Detect Gleason Score Upgrading during Active Surveillance for Men with Low versus Intermediate Risk Prostate Cancer. J Urol. 2017;197(3 Pt 1):632-9.

25. Walton Diaz A, Shrik GA, Lawrentschuk N, Klotz L, Haider M, Hersey K, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. J Urol. 2012;187:1247-52.

26. Frye TP, George AK, Klichevsky A, Maruf M, Siddiqui MM, Kongsuy M, et al. Magnetic Resonance Imaging-Transrectal Ultrasound Guided Fusion Biopsy to Detect Progression in Patients with Existing Lesions on Active Surveillance for Low and Intermediate Risk Prostate Cancer. J Urol. 2017;197(3 Pt 1):640-6.
27. Smith CP, Harmon SA, Barrett T, BittencourtLK, Law YM, Shebel H, et al. Intra- and interreader reproducibility of PI-RADSv2: A multireader study. J Magn Reson Imaging. 2019;49:1694-1703.

28. Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? Eur Urol. 2018;74:48-54.

29. Lebastchi AH, Pinto PA. The role of multiparametric MRI in biopsy-naive prostate cancer. Nat Rev Urol. 2019;16:276-7.

30. Ahdoot M, Lebastchi AH, Turkbey B, Wood B, Pinto PA. Contemporary treatments in prostate cancer focal therapy. Curr Opin Oncol. 2019;31:200-6.

31. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol. 2015;67:771-7.

32. Eggener SE, Scardino PT, Carroll PR, Zelefsky MJ, Sartor O, Hricak H, et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol. 2007;178:2260-7.

33. Wise AM, Stamey TA, McNeal JE, Clayton JL. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology. 2002;60:264-9.

34. Mouraviev V, Mayes JM, Polascik TJ. Pathologic basis of focal therapy for early-stage prostate cancer. Nat Rev Urol. 2009;6:205-15.

35. Villers A, McNeal JE, Freiha FS, Stamey TA. Multiple cancers in the prostate. Morphologic features of clinically recognized versus incidental tumors. Cancer. 1992;70:2313-8.

36. Gill IS, Azzouzi AR, Emberton M, Coleman JA, Coeytaux E, Scherz A, et al. Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Followup and Analyses of Effectiveness. J Urol. 2018;200:786-93.

37. Van der Poel HG, van den Bergh RCN, Briers E, Comford P, Govorov A, Henry AM, et al. Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018. Eur Urol. 2018;74:84-91.

38. Barkin J. High intensity focused ultrasound (HIFU). Can J Urol. 2011;18:5634-43.

39. Truesdale MD, Cheetham PJ, Hruby GW, Wenske S, Conforto AK, Cooper AB, et al. An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: recommendations for follow up. Cancer J. 2010;16:544-9.

40. Bahn D, de Castro Abreu AL, Gill IS, Hung AJ, Silverman P, Gross ME, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol. 2012;62:55-63.

41. Barqawi AB, Stoimenova D, Krughoff K, Eid K, O’Donnell C, Phillips JM, et al. Targeted focal therapy for the management of organ confined prostate cancer. J Urol. 2014;192:749-53.

42. Ellis DS, Manny TB Jr, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. Urology. 2007;70(6 Suppl):9-15.

43. Hale Z, Miyake M, Palacios DA, Rosser CJ. Focal cryosurgical ablation of the prostate: a single institute’s perspective. BMC Urol. 2013;13:2.

44. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The “male lumpectomy”: focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urol Oncol. 2008;26:500-5.

45. Durand M, Barret E, Galiano M, Rozet F, Sanchez-Salas R, Ahallal Y, et al. Focal cryoablation: a treatment option for unilateral low-risk prostate cancer. BJU Int. 2014;113:56-64.

46. Valerio M, Shah TT, Shah P, Mc Cartan N, Emberton M, Arya M, et al. Magnetic resonance imaging-transrectal ultrasound fusion focal cryotherapy of the prostate: A prospective development study. Urol Oncol. 2017;35:150.e1-150.e7.

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