

Active Surveillance for Low-Risk Prostate Cancer: Selection Criteria and Follow-up Plan

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Introduction:

The incidence of prostate cancer detection has more than doubled since the wide acceptance of the serum Prostate-Specific Antigen (PSA) test as a screening tool. There is a possibility that many of the PSA screen detected cases are over-detections with subsequent over-treatments. The rate of over-detections is estimated to be as high as 56% (Etzioni: J. NCI. 94, 2002). Still many men are undergoing standard treatments, such as surgery, robotic surgery, external beam radiation, brachytherapy, and androgen ablation therapy. These are invariably associated with jeopardizing quality of life, mainly urinary and sexual functions. Lately, active surveillance (AS) has become a more accepted management strategy for certain men with low-risk disease. Several studies revealed that AS in the management of low-risk patients resulted in fairly acceptable outcomes, with only a limited number of patients requiring additional treatment. Barocas et. al. reported a review of 1,886 men with prostate cancer of which 16.3% were classified as low-risk cases using Epstein surveillance criteria (PSA <10, Stage <T2a, PSA density <0.15, number of positive tissue cores <33%, absence of Gleason pattern 4 and 5). Only 9% of men with known low-risk disease chose AS. A recent publication (Gorin & Soloway, Urology, Jan 2011) demonstrated that patients are heavily influenced by physicians in their decision to elect AS. Notably, the majority of the patients were not offered AS at diagnosis.

Pros and Cons of AS:

The main advantage of AS is an avoidance of the collateral damage and loss of function that are associated with a decrease in the quality of life. Another advantage would be an overall lower cost to society by not having an expensive medical procedure and not losing productivity. The possibility of losing a "window of opportunity" to cure the disease is the main disadvantage of AS. Therefore, it is extremely important to carefully identify patients with low-risk disease, adhere to close monitoring and proper intervention if there is any evidence of cancer progression. Unfortunately, there is no agreed upon or validated patient stratification method yet. Another disadvantage would be the perceived psychological burden with AS. However, a few studies, mainly by European researchers, revealed that there was no difference in the psychological well being between the AS group and the group with treatment.

Selection Criteria for AS (Bahn Criteria of Perfect 10):

Low Risk Disease (Perfect 10) Bahn's Criteria for Active Surveillance

1. Gleason 6 or less, may be up to 7=3+4
2. PSA less than 10 ng/mL (PSA Density < 0.15)
3. Stage: T1c -T2a, T2b with co-morbidity
4. Positive Biopsy Cores: less than 1/3 of cores
5. Percentage of tumor invasion: less than 50%
6. PSA doubling time: > 2 yrs, prefer >3 yrs.
7. Tumor neovascularity on color-Doppler: 1+ or less
8. Tumor volume on CD-TRUS: less than 1cc
9. Urine PCA-3 gene test: less than 35 (Tumor < 0.5cc)
10. Ploidy: Diploid



Differentiating between low-risk disease that may be indolent for the rest of a patient's life and immediate- or high-risk disease that may be life threatening prostate cancer is quite a difficult task. I have developed more extensive and stringent criteria than most physicians use as a low risk stratification (ex: D'Amico Criteria: PSA <10, Gleason <7, Stage <T2a, Epstein Criteria: see the Introduction)

1. Gleason Grade 6 or less. In some cases, Gleason 7= 3 + 4 may be acceptable if accompanied by significant medical co-morbidity or short life expectancy (less than 10 years). Gleason grade is proven to be one of most important independent predictors for cancer aggressiveness and final outcome.
2. Serum PSA level < 10ng/ml. I prefer to use PSA density <0.15 instead: (PSA density= Serum PSA/Prostate Volume), because PSA is produced by normal prostate glandular tissue as well as cancerous tissue. Large prostate gland is often associated with high PSA as a normal. Other main influences to PSA would be underlying prostatitis that may be the reason for a high PSA and also a fluctuating PSA.
3. Stage: T1c (cancer not felt by DRE nor seen on ultrasound, but needle biopsy is positive) to T2a (cancer is in ½ or less of one side, either in the right or left lobe and is either felt by DRE or seen on ultrasound). T2b (cancer is in more than ½ of one side) or even T2c (cancer is in both lobes) with co-morbidity or a short life expectancy. This stage used is based on a systemic biopsy, not by a color-Doppler US guided target biopsy. A target biopsy usually takes a fewer number of biopsy cores, but diagnoses 2-3 times more cancer than a systemic biopsy. It also comes with a

higher Gleason grade and a higher stage of disease. It is not uncommon to see a systemic biopsy actually underestimate and under-stage a cancer.

4. Positive biopsy core number: less than 1/3 of total cores taken. It is a general observation that a higher number of positive tissue cores among biopsy specimens is associated with a larger volume cancer with advanced stage.
5. Percentage of tumor invasion seen in biopsy tissue core: less than 50% in any one core. The same logic is applied here as with number of biopsy cores.
6. PSA doubling time: more than 2 years, prefer more than 3 years. PSA doubling time may indicate the time needed for the tumor double in size. Dr. Klotz's landmark paper on AS study showed only two deaths out of almost 300 men with AS. These two patients had a PSA doubling time of less than 2 years.
7. Tumor neovascularity (abnormally increased blood supply) on color-Doppler US: 1+ or less. It is known that the higher the abnormal blood supply to the tumor mass, the higher the Gleason grade tumor with aggressive biological behavior.
8. Tumor volume measured by color-Doppler US: less than 1 cc. The larger the tumor volume, especially in the peripheral zone of the prostate, the greater the chance to have an extracapsular penetration of the tumor escape towards the nearby neurovascular bundles or to the seminal vesicles (becoming T3 stage). The tumor in the transition zone is often detected when it is large and still contained in the prostate. The transition tumor seems to have less aggressive biological behavior than the peripheral zone tumor. A small volume tumor in the transition zone with Gleason 6 would be a good cancer to watch.
9. Urine PCA-3 gene test: less than 35. Recently developed Prostate Cancer Antigen 3 (PCA-3) is considered to be prostate cancer specific and highly over expressed in cancer. Multiple papers were published to identify the sensitivity for positive biopsy. Even though there are controversies, a high PCA-3 result (especially >100) was related to a positive biopsy. In addition, PCA-3 scores were significantly lower in low-volume and clinically insignificant prostate cancers. Ploussard (Eur Urol. Dec. 2010) reported a strong correlation between the PCA-3 score and tumor volume. The risk of having a significant cancer that is larger than 0.5 cm³ was increased threefold in men with a PCA-3 score of >25 compared to men with a PCA-3 score of <25. It is also suggested by some researchers that it can be used as a tumor marker (same as PSA) in cancer management.
10. Ploidy: Diploid. Measurement of the nuclear DNA content allows classification of human cancers as either diploid or aneuploid. This test is performed with biopsy tissue specimens. Even though its popularity has faded lately, it may be added information that a cancer would indeed be low-risk disease. There are many reports supporting evidence for favorable survival in prostate patients with DNA diploid tumors.

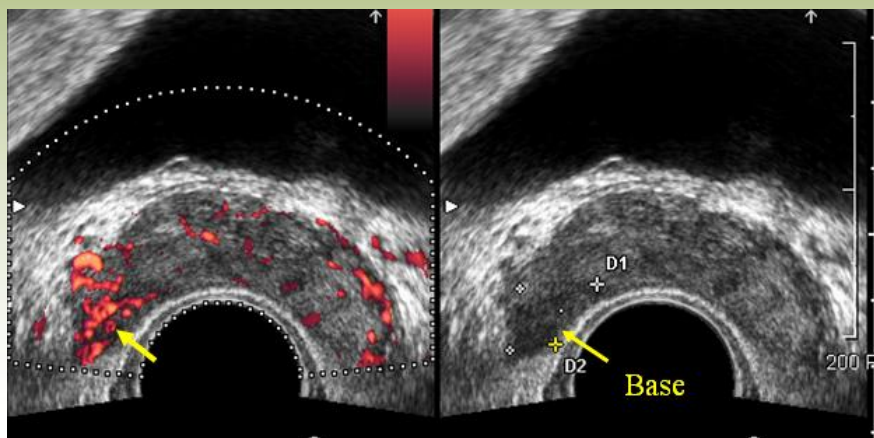
If a patient's cancer features meet all 10 criteria (they receive a perfect 10 score), it would indeed be low-risk, probably clinically not a significant cancer and requires no aggressive treatment. In this case, AS is justified and encouraged. The first 6 criteria in this list are more important than the rest. If a patient's cancer does not meet more than 6 criteria, it could be considered as an intermediate or even a high-risk disease. A recent study by Cooperberg, et al (J Clin Oncol, Jan. 2011) reviewed AS outcome data in a low-risk versus an intermediate-risk group. The conclusion was "Selected men with intermediate-risk features be appropriate for AS, and are not necessarily more likely to progress. AS for these men may provide an opportunity to further reduce overtreatment of disease that is unlikely to progress to advanced cancer."

Role of color-Doppler Transrectal Ultrasound (CD-TRUS) :

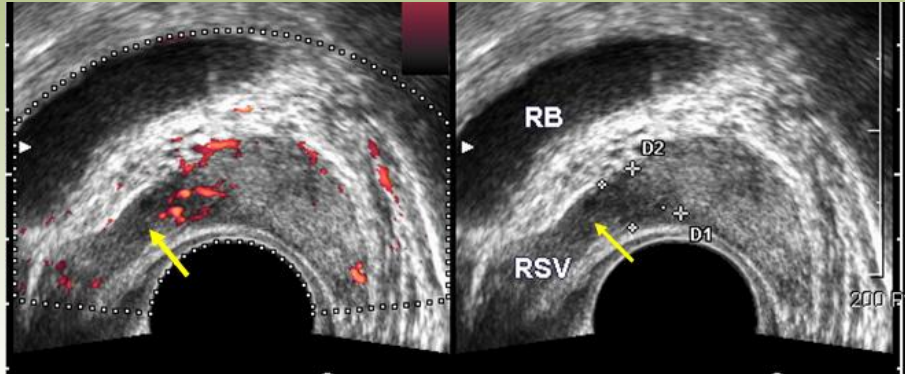
It is extremely important to have an accurate Gleason grade, cancer stage, cancer location, cancer volume, and cancer vascularity to access the risk stratification by using the perfect 10 criteria. In case we use under-staged or under-estimated data from a random systemic biopsy, it may end up with choosing an inappropriate cancer management option with subsequent failure. Further investigation with CD-TRUS with targeted and staging biopsy would limit this mistake. The tumor volume by CD-TRUS measurement is usually larger than conventional black and white (Grey scale) ultrasound and the tumor neovascularity can be measured only when CD-TRUS technology is applied. Here is a good example:

Base Tumor: Mr.W, 68 yrs. PSA 4.0, Gleason 6, T1c

**Recommended RP or AS
TRUS: Hypoechoic lesion in RB, Neovascularity**



Mr. W: Re-biopsy: Gleason 7, RB & RSV Stage: T3b (up staged from T1c)



Mr. W: His cancer was diagnosed as Gleason grade 6, as seen in one of 12 systemic biopsy tissue cores. It was staged as T1c. With a PSA of 4 ng/mL, it was classified as a low-risk disease and he was offered AS along with other aggressive therapy including radical prostatectomy. He made up his mind for AS and wanted to have a CD-TRUD to establish a new baseline for future reference. The CD-TRUS revealed a more than 1cc size, highly vascular tumor at the right base portion of the prostate with possible right seminal vesicle (RSV) invasion. A targeted and staging biopsy was performed and confirmed that it was a Gleason 7=4+3 tumor with right seminal vesicle invasion. The percentage of the tumor in the specimen was also larger than the original biopsy. His cancer was re-staged as a T3b upstaged from T1c. A cancer with a T3b stage is considered as a locally advanced disease and belongs to the high-risk category. Definitely, he was not a candidate for AS and he may not be a good candidate for radical surgery as well, due to the seminal vesicle invasion. He had to reconsider all the definite cancer treatment options carefully.

Published outcomes with AS:

Klotz and Choo were the first to report on prospective AS results. With a median follow-up of 72 months, 34% came off AS (101/331 patients). The reasons were a rapid PSA rise (15%), clinical progression (3%), histological progression (4%), and patient preference (12%). The overall survival rate was 85% and the disease-specific survival rate was 99%. The triggers for leaving AS included: DRE becoming positive, PSA rising with a doubling time of less than 3 years, and a follow-up biopsy showing cancer with a Gleason 7=4+3 or higher. It is my opinion that if all of the patients underwent CD-TRUS with a proper staging biopsy at the time of the initial diagnosis, some of these men would have not been a candidate for AS. Several other publications including

Klotz's updated data are similar to this report. Interestingly, data from the Swedish researchers and Memorial Sloan-Kettering did not find differences in outcomes between immediate radical prostatectomy (RP) and delayed RP (after leaving AS) in the low-risk disease group.

Follow-up schedule:

There is no agreed upon strategy for managing patients. However, these are the general guidelines used in most practices.

- A PSA every 3 months for 2 years, then every 6 months assuming the PSA is stable.
- A follow-up biopsy (preferably a target biopsy) at one year and then every 3-5 years until age 80, assuming that the follow-up PSAs remain stable.
- A CD-TRUS on alternate visits along with a DRE.

Recently, the urine PCA-3 test was proposed as a tumor marker as in PSA in the management of AS. It is still too early to recommend this as a routine practice. More studies are needed.

In addition to a CD-TRUS to objectively monitor the known cancer, other imaging modalities, especially contrast enhanced & diffusion weighed MRI could be used to monitor the cancer.

Moving from Active Surveillance to Growth Arrest:

Dr. Charles Meyers developed an interesting concept that would be beneficial to men with AS. He recommends good diet, supplements and proper exercise that will likely to improve a man's general health. Most men with low-risk prostate cancer die from reasons other than prostate cancer, such as heart attacks, strokes, diabetes and colon cancer. He recommends:

- Avodart or Proscar
- A Mediterranean heart healthy diet
- Exercise
- Reverse vitamin D deficiency
- Pomegranate juice or extract capsules
- Lycopene
- Fish or fish oil
- Antioxidants
- And to aggressively treat hypertension, high cholesterol and high blood pressure, reverse obesity, and timely colonoscopies.

One paper was recently published with the goal of determining the effect of Proscar or Avodart on pathologic progression in men on AS (Finelli et al. Eur Urol Dec. 2010). 93/288 men (32%) experienced pathologic progression and abandoned AS during a median follow-up of 38.5 months. Men taking Avodart or Proscar experienced a lower rate of pathologic progression (18.6% vs 36.7%) and were less likely to abandon AS.

Focal Therapy for Prostate Cancer:

Focal therapy for localized prostate cancer has gained in popularity recently. Cryoablation is a commonly used technology. Multiple single institution reports show good cancer control with minimal side effects. Bahn reported 0% urinary incontinence and 10% sexual dysfunction (J Endourology 2006). Current standard care options are either AS or radical treatment. Focal therapy would be a good compromise, middle ground approach. It may avoid both under- or over-treatment. It is important to have a unifocal or unilateral disease to consider this option. In case of a significant psychological burden with AS or the identification of minimal disease progression during AS management, focal therapy could be a reasonable choice. Precise identification of the cancer location, size and extent by CD-TRUS is extremely important to perform a target freezing procedure that is done under TRUS guidance.

Conclusion:

We have experienced a great prostate cancer stage migration during the last two decades. The debate on over-detection and over-treatment of prostate cancer is still ongoing. AS became an increasingly popular option for selected men. It appears to be proven safe in the intermediate time frame. Selection criteria, a follow-up plan and triggers for intervention were discussed. The role of CD-TRUS in the identification of an AS candidate and in the follow-up management was also addressed. There is an interesting concept of "Moving AS to Growth Arrest" by using Avodart or Proscar as a main ingredient. If a patient is uncomfortable with AS and also uncomfortable with radical therapy, or disease progression is confirmed during the course of AS management, focal therapy could be an option as a minimally invasive treatment. Unfortunately, most patients with low-risk disease are not offered Active Surveillance as an option. There is a need for proper public education and patient empowerment.