

# Active Surveillance with High Resolution Color-Doppler Transrectal Ultrasound Monitoring: *Is it fool-proof?*

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## INTRODUCTION

In the November 2006 issue of *Insights*, there was an excellent article by Dr. Laurence Klotz, entitled “Active Surveillance (AS) for Favorable Risk Prostate Cancer”. This article clearly stated that there are many men who have been or will be diagnosed with prostate cancer that does not pose a threat to their lives. In the Finasteride prevention trial, 24% of men undergoing a random sextant biopsy with normal PSA levels were diagnosed with prostate cancer<sup>1</sup>. It is well recognized that we may over-detecting and over-treating prostate cancer. Draisma, et al reported an over-detection rate of 48% in their series, and the reported range of the over- detection rate was 16-56%<sup>2</sup>. This is due to increased awareness of prostate cancer with easy access to PSA and ultrasound guided transrectal biopsy. When Bill-Axelsson, et al monitored 348 men with intermediate risk disease, the 10-year mortality rate was only 15%. They also stated that patents with low-risk disease or without extended life expectancy may not benefit from treatment<sup>3</sup>.

**In the U.S., 75% of men 75 years or older with low risk disease undergo local treatment rather than pursue an Active Surveillance(AS) program.** CaPSURE data shows that 94% of men with low-risk prostate cancer received radical treatment<sup>4</sup>. Overall, the lifetime risk of dying from prostate cancer remains less than 3%<sup>5</sup>.

Watchful waiting (WW) is a widely accepted treatment for older men with prostate cancer. Since prostate cancer typically involves a slow-growing tumor, several decades often pass before it becomes a life-threatening disease. Traditionally, WW means not considering any local treatment such as surgery or radiation and initiating androgen deprivation therapy when clinical symptoms develop.

The concept of AS is different from that of WW. The strategy of AS is not to forgo radical local treatment altogether. rather it is to delay the treatment as long as possible and to offer treatment only when disease progression is confirmed during close clinical observation<sup>6,7</sup>. Most importantly, one should not lose the window of opportunity for successful local therapy.

The selection criteria for AS as applied to low risk disease continue to evolve.. The clinical parameters used to predict cancer aggressiveness are PSA, Gleason score, and tumor stage. Favorable risk (low-risk) prostate cancer is characterized as a PSA of 10 or less, a Gleason 6 or less, and T1c – T2a disease<sup>8</sup>. For patients over age 70, the criteria are typically somewhat relaxed. Choo et al allowed patients with a Gleason grade up to 7 (3 + 4) and a PSA up to 15 to have AS<sup>9,10</sup>. Factors such as percent of positive tissue cores (fifty percent or more cores positive), or a PSA velocity above 2 ng/year, are signs of more aggressive disease, suggesting the need for a definite treatment rather than AS<sup>11</sup>.

Using selection criteria of this nature, preliminary results from prospective trial of AS in 299 men has produced encouraging results. Klotz reported a disease-specific

survival rate of 99% at eight years out<sup>12</sup>. Only two men died as a result of prostate cancer, and they had PSA doubling times of less than two years. However, 22% of the patients in this group revealed either biochemical progression, clinical progression, or histological progression of the disease during AS, and they were subsequently treated properly. This 22% of the patient population may have been under-staged at the time of the diagnosis and probably were not candidates for AS from the beginning.

Despite this encouraging result, there is the sobering reality of 30,000 prostate cancer death in the US each year. **We may mistakenly recommend AS to a man with high-risk disease, delaying potentially curative therapy and losing the window of opportunity for effective treatment.** Reliance on state-of-the-art imaging may help to reduce some of this dangerous staging error.

Transrectal ultrasound was introduced as a prostate cancer screening and diagnostic tool in the 1980s, but the results were disappointing. However, there has since been significant improvement in ultrasound technology, particularly during the last decade. High resolution, color-Doppler Ultrasound (HR-CDU) and tissue harmonic technology has improved the cancer detection. In addition, a specific lesion-directed target biopsy along with the biopsy of potential route of tumor escape (such as near-by neurovascular bundle and seminal vesicles) improved staging of the cancer and often improved Gleason grading. **Our previously published study showed that 26 % of the patients were up-staged to T3 –T4 from T1 – T2 stage when targeted and staging biopsies were used**<sup>13</sup>. Familiarity with the capabilities and benefits of HR-CDU technology, when coupled with lesion directed and staging biopsy, seems to be lacking to many clinicians.

This article highlights the potential benefits of an HR-CDU, especially to a man who is considering AS or who has been on AS, as an added information and a confirmation to be a proper candidate.

## **MATERIALS AND METHODS**

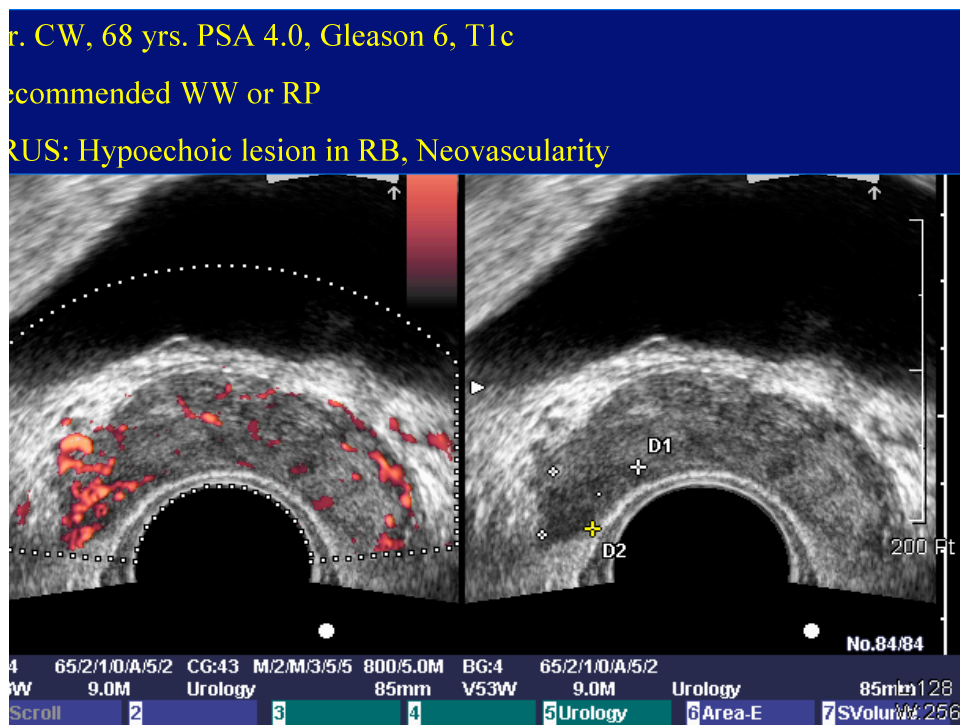
Cases were selected for presentation to illustrate the clinical impact of an HR-CDU and directed biopsy on men who are considering AS or who have been on AS after there was an initial diagnosis of prostate cancer by a conventional systemic, random, blind biopsy. Significant additional information was detected in many cases that led to drastic changes in management of the disease.

All studies were performed on Hitachi EUB-6500. The ultrasound probe used was an end-firing, trans-vaginal probe utilizing 5-9 MHz. the prostate gland was scanned from seminal vesicles down to the mid gland, to the apex, and to the level of the external sphincter in the axial and sagittal planes. Color-Doppler (Power Doppler) and tissue harmonic technology was used to improve the spatial and contrast resolution. Color-Doppler (power-Doppler) and gray-scale images were displayed simultaneously on a high-resolution monitor for the operator to view, and an extra monitor was placed in front of patient for his viewing. During the examination, there was a constant communication between the operator and the patient to explain the anatomy, the characteristics of the lesion(s), and any possible limitations and ramifications with each treatment options related to the cancer identified on the ultrasound images.

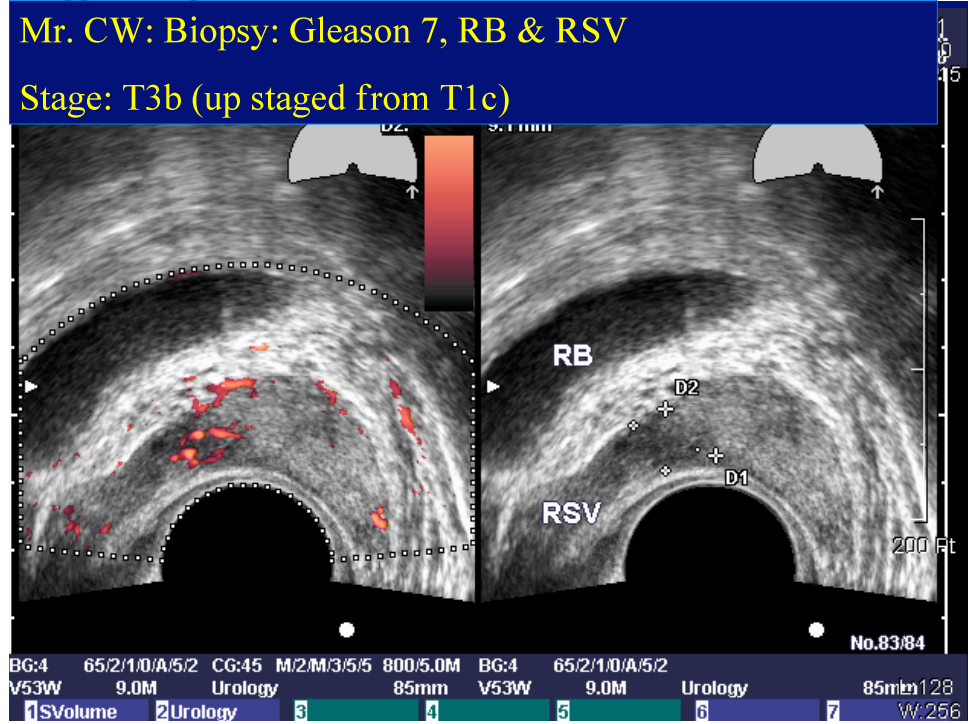
After the HR-CDU examination, the patient and his family members returned to the office and discussed in detail the ultrasound findings and managerial options shown on laser-printed color-Doppler images. Patients left the office with a set of color-Doppler images and a preliminary report. They also received a formal written ultrasound report by mail (as did his physicians). In cases where a biopsy was performed, a personal phone call was made to discuss the result as soon as pathology report is received.

## RESULTS

**CASE #1 :** Mr CW is a 68-year-old man with a PSA of 4.0 and a non-specific digital rectal examination. A routine eight-core biopsy showed a Gleason 6 malignancy in one core from the right lobe. The exact location of the tumor in the right lobe was unknown. The clinical stage was T1c. Multiple consultations were obtained. He was told that he could watch his cancer with PSA surveillance; if not, he would be a good candidate for radiation therapy or radical prostatectomy. The patient was leaning towards AS, since all the clinical parameters were favorable for low-risk disease. Then, HR-CDU imaging was performed and it showed a 18 mm x 12 mm, hypoechoic lesion in the right lobe with significantly increased blood flow that was suggestive of neovascularity. The lesion was close to the right seminal vesicle with an actual invasion. Directed and staging biopsies were performed, and they confirmed Gleason 6 cancer involving the right base and right seminal vesicle. The clinical stage was upstaged to T3b. AS was not recommended, and the patient received a proper treatment.



Axial view: A gray-scale ultrasound image (at the left) shows a dark lesion (marked by the cursor) that was suspicious for known cancer by original biopsy. A Color-Doppler ultrasound image (at the right) shows that the lesion receives much more blood flow (neovascularity) than the rest of the normal tissue. This suggests that it is most likely is an aggressive prostate cancer.



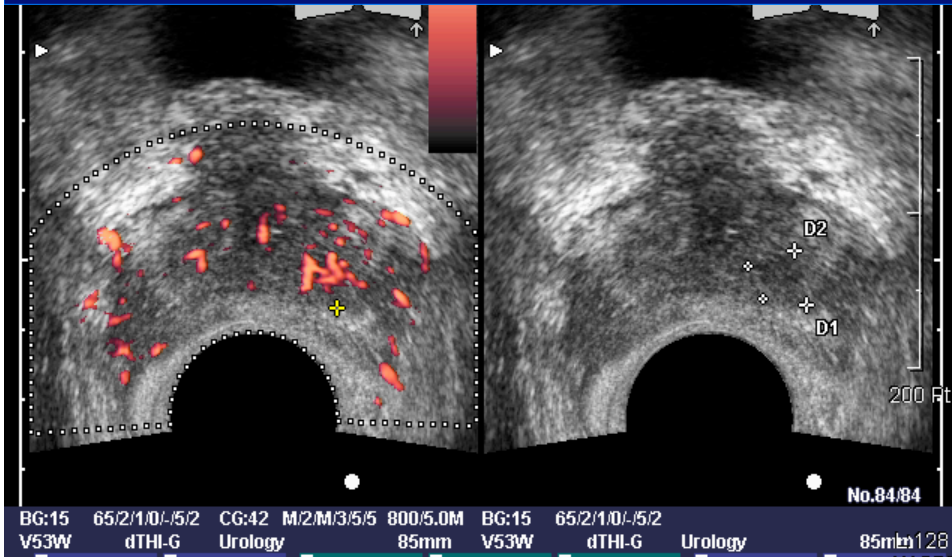
Sagittal view: The gray-scale image (at the left) shows a dark spot (at the cursor) at the base portion of the prostate (the same lesion that is seen on the axial projection) with neovascularity. It is close to the right seminal vesicle (RSV), suggestive of an actual invasion of the cancer into the seminal vesicle.

**CASE #2** : Dr. CF is 67-year-old man who had a PSA 8 with significant BPH (benign prostatic hyperplasia). Due to the BPH, the PSA level was still within the predicted range. A 12-core biopsy performed by his physician showed no evidence of cancer. However, he subsequently had HD-CDU that showed a 5 mm x 5 mm hypoechoic lesion in the left apex transition zone. Actually, it was detected in retrospective observation in gray scale, but only after the color-Doppler detected a local area of increased blood flow. A directed biopsy confirmed that Gleason 6 cancer. With the known size of the tumor (less than 1cc), a Gleason 6, and a transition zone location, he was confirmed to be a good candidate for AS. The patient and his physician agreed upon a program of AS with close PSA watch and follow-up HR-CDU to objectively monitor the tumor volume. His cancer volume and his PSA have remained stable for several years.

Dr. CF, 68 yrs. PSA 8 (was 4-5 range more than 4 years)

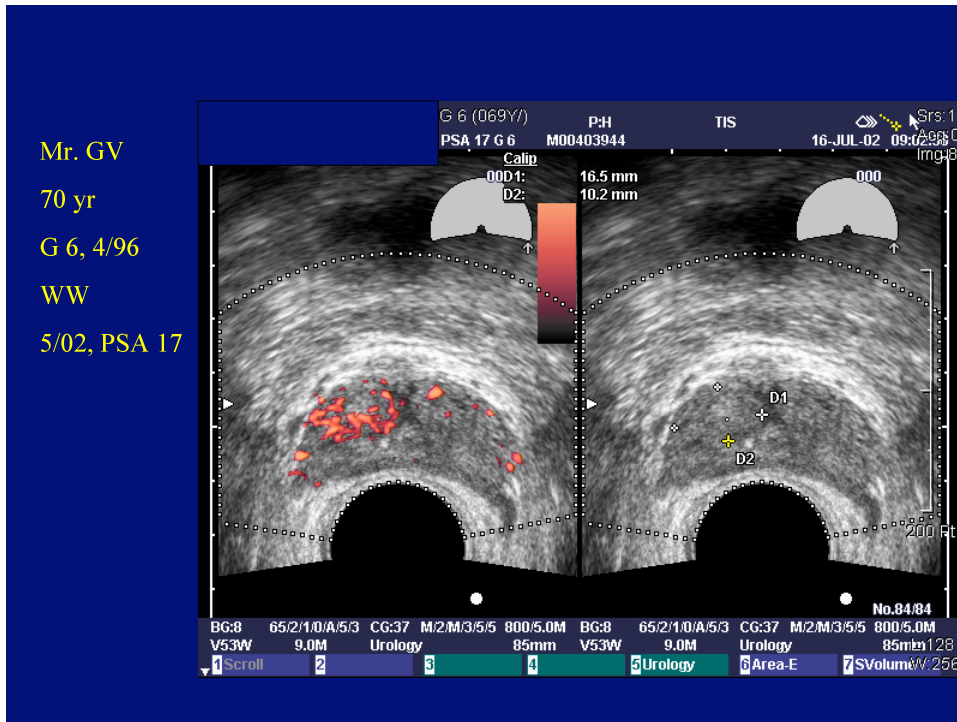
12 Cores Biopsy: Negative

Color-Doppler TRUS: LATZ lesion, G6



The Color-Doppler image (at the left) clearly shows a small focal area of increased blood flow. the gray-scale image (at the right) shows a subtle dark spot that corresponds to the color-Doppler finding. It was actually picked up in retrospective observation, located upon seeing the color image.

**CASE #3** : Mr. GV is 70-year-old man whose Gleason 6 cancer was diagnosed in 1996. He has been on WW since then. In May 2002, he came to me for an HR-CDU to re-evaluate his cancer because his most recent PSA level had risen to 12, up from 10 a year ago and up from 7.5 in 1996. A gray scale ultrasound was entirely normal. (The tumor was iso-echoic, which means that the tissue texture is identical to the back ground normal tissue.) However, the color-Doppler study clearly depicted a large, 17 x 10 mm lesion with intense neovascularity in the right apex. Even though a large transition zone cancer with a high PSA and may still be contained within the prostate (contrary to peripheral zone cancer), we recommended that this patient seek a proper treatment rather than staying on WW. The recent PSA elevating trend, the large volume tumor, and the intense neovascularity created an unfavorable risk for him.



Only the color image (at the left) depicts a lesion with increased blood flow (neovascularity). the gray-scale image does not show any abnormality, even with retrospective observation.

## DISCUSSION

With the down-stage (risk) migration of prostate cancer we have seen lately<sup>14</sup>, AS has become an attractive option to many men who are *assumed* to have early-stage, low-risk disease. It allows men to delay surgery, radiation, cryotherapy or androgen deprivation therapy for years. But patients and doctors remain concerned about mis-staging the disease, thereby mistakenly recommending AS when actually occult high-risk disease is present.

Modern HD-CDU imaging offers an improved spatial and contrast resolution that leads to a correct identification of the tumor, the exact location of the tumor, the size of the tumor, and the neovascularity of the tumor. It also enables us to perform a directed target biopsy of the lesion and staging biopsy if we suspect extra-capsular extension of the tumor. By doing so, we can determine an exact pathologic stage rather than just the clinical stage. Along with other clinical parameters, this added information will provide further assurance to men who are considering AS or have been on AS. It is not perfect, but it is the best effort we could exercise. It is a definite benefit to identify the tumor, so it can be monitored objectively on follow-up HD-CDU imaging.

Data on AS based on clinical information is still encouraging. Dr. Klotz's study showed 22% patients with disease progression. It may well represent a natural disease progression rather than a mis-staging at the time of diagnosis. However, if an HD-CDU

was utilized along with directed and staging biopsies, many men in this group might have proven not to be a candidate for AS.

That under-staging often occurs with the standard 8-12 core biopsy has been well documented in the surgical literature. The frequency of under-staging in men with prostate cancer is so great that under-staging has become a cogent argument against using AS.

The ability of HR-CDU to locate the disease within the prostate has been demonstrated in number of studies. Targeted, directed and staging biopsies find more cancer both inside the prostate and extended outside the capsule with greater frequency than systemic random biopsy. In our experience “upstaging” the cancer with this technique is a relatively common occurrence as the case examples in this article have illustrated. Clearly, pathologic proof of previously unsuspected seminal vesicle invasion, extra-capsular disease, or high Gleason grade disease is a clinically relevant and useful discovery. **It may transfer a patient assumed to have a low-risk disease to one proven to have a low risk disease and hence a good candidate for AS.** It can also be argued that such findings are important even in men unwilling to consider AS as a treatment option. Certainly, selection of the best local therapy can be improved if the presence and location of extraprostatic disease can be ascertained before surgery or radiation.

One might argue that a man opting for AS may take on a significant psychological burden since he is living with known cancer for a long period of time. The alternative of receiving a cancer treatment may reduce the burden, but the side effects and complications of therapy may carry their own psychological burdens. **A recent Swedish study that was randomized trial of observation versus prostatectomy concluded that there was no difference in psychological burden at 5 years<sup>15</sup>.**

That prostate cancer is over treated in the United States is widely acknowledged, but only in the abstract sense. Clinicians, when confronted with living, breathing, and frightened patients seem unable to provide sufficient assurance to their patients that delaying radical treatment truly represents a safe alternative. Hopefully, ongoing improvement in imaging and staging technology can help us to reach the point where sufficient reassurance can be provided, so that the overuse of radical therapy can be reined in. HR-CDU imaging can be used to greatly narrow this gap, although it is not perfect nor foolproof as yet. However, further development in ultrasound technology and the availability of ultrasound contrast medium are expected in near future.

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