Active surveillance for prostate cancer in a veteran population

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Introduction: *Active surveillance for prostate cancer is a therapeutic option which is gaining more popularity. Implicit in this approach is careful monitoring to identify those with progression. Criteria for placing patients on active surveillance vary but generally include Gleason sum of 6 or less, prostate-specific antigen (PSA) less than 20, and a small volume of cancer in the biopsy specimen. We review our experience with active surveillance in a veteran population.*

Materials and methods: *We conducted a retrospective review of patients from the Kansas City Veterans Affairs (KCVA) who met the requirements for active surveillance (Gleason sum 6, percent of cancer in the specimen less than 20%, and PSA less than 20 ng/dL) between January 2004 and December 2009. In the patient group who chose active surveillance (AS), we evaluated the rates of compliance with the protocol mandated PSA's and the 1 year biopsy. In the patient group who declined AS and underwent immediate prostatectomy, we reviewed the final pathology for stage, Gleason grade, percent of tissue involved with cancer, margin status, nodal status, and rates of biochemical recurrence.*

Results: *We identified 207 patients who met the requirements for active surveillance. Of these patients, 45 patients chose active surveillance while 66 patients underwent immediate radical prostatectomy at the KCVA. Of the 45 patients who went on active surveillance, all participants had at least one PSA drawn. However, only 24 (53.3%) patients complied with the protocol mandated prostate biopsy at 1 year. In the patient group who chose to undergo an immediate prostatectomy, 43 of 66 (65.2%) patients had upgrading of their Gleason score. This included 12 patients upgraded to Gleason sum 8 to 10 and two patients who were upstaged to T3 disease. Despite the significant upgrading, only two patients have had a biochemical recurrence at a median follow up of 30 months.*

Conclusions: *Active surveillance is a viable option for patients with low risk prostate cancer. However, this study raises concerns about compliance with recommendations for active surveillance in a VA population. Furthermore, there was a significant risk in this study of under-grading in patients who underwent immediate prostatectomy. This emphasizes the need for better education of patients who enter into active surveillance protocols regarding the need for compliance, the risks of progression, and the chance of under grading.*

Key Words: prostate cancer, active surveillance, pathologic upgrading, compliance

Introduction

The advent of the prostate-specific antigen (PSA) has led to a stage migration towards low stage and low grade prostate cancer. This is supported by the findings of the CaPSURE database in which Cooperberg et al found a decreasing trend of high risk prostate cancer from 36.6% in 1989-1992 to 16.0% in 1999-2002. During the same time frame, low risk prostate cancer went from 29.5% in 1989-1992 to 46.8% in 1999-2002.[1] Despite this trend, it is important to remember that prostate cancer remains the second most common cause of cancer mortality in Caucasian males in the United States accounting for an estimated 28,660 deaths in 2008.[2] Because prostate cancer is an extremely heterogeneous disease and currently there is a lack of predictive biomarkers, many attempts have been made to stratify risk based on clinicopathologic features. This is in an attempt to

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identify those who need definitive treatment, while attempting to avoid potentially morbid therapies in those with clinically insignificant prostate cancer.

Active surveillance is a treatment modality which utilizes the PSA test, clinical stage, biopsy results, as well as repeat biopsies to delay or avoid therapy until there are objective signs of progression. Most protocols for active surveillance use the clinical criteria based on Epstein's paper on insignificant cancer to identify patients. In this article, factors for predicting insignificant prostate cancer include PSA density less than 0.1 ng/mL per gram and no adverse pathologic findings on needle biopsy (Gleason pattern 4 or 5, less than three or more core samples involved, and no core with more than 50% involvement).[3] The most common active surveillance protocols in use today include the Hardie,[4] Klotz,[5] and Choo[6] classifications. Although each vary in definition, they generally include patients with clinical stage T1-T2 disease, PSA less than 20 ng/mL, and biopsy Gleason sum 7 or less. These protocols generally follow patients with PSA's every 3-6 months and repeat a prostate biopsy in 1-2 years. Progression is typically evaluated with PSA doubling time, increased Gleason score on repeat biopsy, and increase in clinical stage. Typically, these patients undergo definitive treatment once progression is determined.

In this study, we report our experience with low grade, low stage prostate cancer in a veteran population. We performed a retrospective review of patients who met criteria for our active surveillance protocol. We determined the rates of compliance with the subsequent PSA tests as well as the compliance with the 1 year repeat ultrasound guided prostate biopsy. Furthermore, we reviewed the rates of progression on follow up biopsies as well as the modality of treatment chosen. We also determined the rates of upstaging and upgrading on final pathology in patients eligible for active surveillance but who chose immediate surgical therapy.

Materials and methods

After Internal Review Board approval was obtained from the Kansas City Veterans Affairs (KCVA) medical center, we performed a retrospective chart review of a comprehensive prostate cancer database. Patients diagnosed with prostate cancer on transrectal ultrasound (TRUS) guided biopsy of the prostate between January 1, 2004 and December 31, 2009 were identified for our analysis. Patients with low risk features who met the criteria for active surveillance were included. Specifically, these patients had clinical stage T2 or less, Gleason sum 6 or less, PSA less than 20, and percent of total tissue on biopsy positive for cancer less than 20%. Specific patient groups were then identified including those who chose active surveillance (n = 45) and those who chose immediate RRP at the KCVA (n = 66).

All TRUS guided biopsies of the prostate were performed using a standard 12-core biopsy scheme, however, an increased number of biopsies were taken for larger glands at the discretion of the physician performing the biopsy. Pathologic examination of the tissue was performed by one of five full-time KCVA pathologists. Gleason sum was reported in the standard fashion with the most common Gleason score added to the second most common Gleason score, with note being made of any pattern 5. The amount of cancer in the biopsy specimen was reported as a total percentage of the biopsy tissue. For the purposes of this study we chose a cutoff of 20% or less of the tissue being involved with cancer as criteria for active surveillance.

This was extrapolated from other protocols which include patients with no more than one of three cores positive and no more than 50% of any core involved with cancer. Therefore, if a patient has one of three cores with 50% involved with cancer, it equates to a total of 16.7% of the total tissue involved with cancer.

For the patients who chose to undergo our active surveillance protocol during this time frame, we recommended PSAs drawn every 3 months and a repeat ultrasound guided prostate biopsy at 1 year. Our primary endpoint was to evaluate the compliance with the PSA lab draws and the protocol mandated 1 year repeat prostate biopsy. The pathology reports of the repeat biopsies were then evaluated for rates of upgrading or increased tumor volume. Rates of dropout from active surveillance as well as the types of definitive therapy the patient chose eventually were reviewed.

For the patient population who met our criteria for active surveillance but chose to undergo immediate RRP, final pathology reports were reviewed for Gleason grade, pathologic stage, nodal status, margin status, and percentage of prostate involved with cancer. As a subset of our RRP population, we also examined a subset using more stringent requirements for active surveillance. We identified those patients with Gleason sum of 6, PSA less than 10 ng/dL, percent cancer in biopsy < 20%, and PSA density less than 0.15 ng/mL^2 who went on to radical prostatectomy.

Rates of biochemical recurrence and rates of salvage therapy were also identified from the database and reported as a percentage of the whole. Statistical analysis was not performed as this is an observational report and there were no comparison groups.

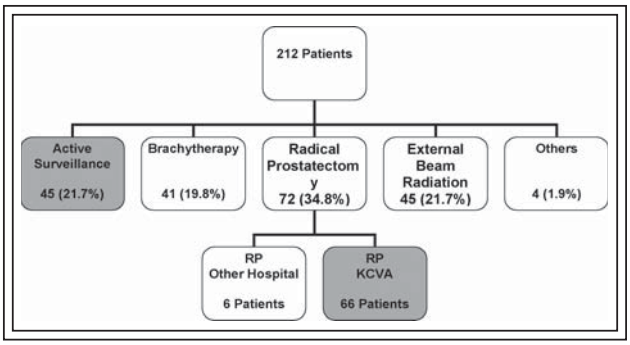

Figure 1. Flowchart of patients meeting criteria for active surveillance.

Results

There were a total of 207 patients who were diagnosed with prostate cancer that met the criteria for active surveillance between January 1, 2004 and December 31, 2009. Of these patients, 41 (19.8%) underwent brachytherapy, 45 (21.7%) had external beam radiation, 45 (21.7%) chose active surveillance, and 72 (34.8%) went on to radical prostatectomy. The two groups of patients featured in our study are shaded in Figure 1.

Clinicopathologic characteristics of the 45 patients who elected to undergo active surveillance are shown in Table 1. Our analysis was performed at a mean follow up of 23.8 months. Of the 45 patients included, all 45 (100%) had at least one PSA result after starting the active surveillance protocol. However, only 24/45 (53.3%) of the patients agreed and/or complied to undergo the protocol mandated 1 year ultrasound guided prostate biopsy. Among the patients who underwent the biopsy, 6/24 (25%) of patients had a negative biopsy, 11/24 (45.8%) of patients had similar grade and percent cancer from their initial biopsy, and 7/24 (29.2%) had upgrading. Also, of the patients who underwent a repeat biopsy, 17/24 (70.8%) continued on with active surveillance while 6/24 (25%) had radiation and 1/24 (4.2%%) had a radical prostatectomy.

TABLE 1. **Patients on active surveillance (total 45 patients)**

	Mean	Median	Range
Age (years)	72.3	73	55-85
Gleason sum (biopsy)	6	6	6
Percent cancer (biopsy)	4.4	2	1-20
PSA (prebiopsy)	6.4	5.7	3.0-17.3
Follow up (months)	23.8	19.0	6-58

TABLE 2. **Patients undergoing immediate postbiopsy radical prostatectomy at the KCVA**

	Mean	Median	Range
Age (years)	62.0	61.0	48-79
Ultrasound measured prostate volume (cc)	35.4	32.0	11-110
Number of cores on biopsy	13.5	12.0	8-24
TRUS biopsy Gleason sum	6	6	6
Prebiopsy PSA	6.3	5.8	0.8-15.8
% of biopsy involved with cancer	6.6	5.0	1-20

Of the 72 patients who underwent immediate radical prostatectomy after diagnosis of prostate cancer, 66 patients had their radical prostatectomy performed at the KCVA while six patients had their operation at an outside facility. The 66 men who had surgery at the KCVA make up our second study population. Prebiopsy PSA, TRUS measured prostate size, number of core biopsies, and percentage of tissue involved with cancer are included in Table 2. Similar data for the men who underwent radical prostatectomy at outside institutions are included in Table 3 and are similar to the study population.

The final prostatectomy pathology of the 66 patients is shown in Table 4. Interestingly, 43/66 (65.2%) patients had upgrading from Gleason sum of 6 to higher grade cancer. Thirty-one (47.0%) patients were upgraded to Gleason sum 7 of which 30/31 were Gleason 3 + 4 and one patient had Gleason 4 + 3. Twelve

TABLE 3. **Patients undergoing immediate postbiopsy radical prostatectomy at outside institutions**

	Mean	Median	Range
Age (years)	64.8	62.5	57-77
Ultrasound measured prostate volume (cc)	34.7	30.0	18-58
Number of cores on biopsy	13	12	12-16
TRUS biopsy Gleason sum	6	6	6
Prebiopsy PSA	4.7	5.1	1.9-6.1
% of biopsy involved with cancer	7.2	5.0	4-20

TABLE 4. **Radical prostatectomy pathology (66 patients)**

Gleason	Gleason sum 5-6 23 (34.9%)	Gleason sum 7 31 (47.0%)	Gleason sum 8-10 12 (18.2%)
Stage	T2 64/66 (97.0%)	T3 2/66 (3.0%)	
Margin status	Positive 10 (15.2%)	Negative 56 (84.8%)	
Lymph node status	Number of patients undergoing LAD 58 (87.9%)	Number of nodes mean/median/range 5.5/4.2/0-19	Number of positive nodes 0
Percentage of tissue involved with cancer	Mean 8.7	Median 5	Range 1-40

(18.2%) patients had upgrading to Gleason sum 8 to 10 with one patient having primary Gleason score 5. All three patients who had PSA greater than 10 had either primary or secondary Gleason score 5.

A minority of patients, 2/66 (3.0%) had upstaging to T3 disease. Of these two patients, both also had upgrading, with one patient having primary Gleason 5 and the other having secondary Gleason 5 on final pathology. A total of 10 men (15.2%) had positive margins on the prostatectomy specimen. Of the 10 patients who had positive margins, eight patients had upgrading on final pathology. The average percent of tissue involved with cancer on final pathology was 8.7% compared to the percentage of cancer on biopsy of 6.6%. Pelvic lymphadenectomy was performed in 58 patients who underwent an RRP with the average lymph node yield being 5.48. There were no positive lymph nodes on final pathology.

At a median follow up of 30 months, only two patients had experienced a biochemical recurrence at 43 and 51 months, respectively. Both of these patients were treated with salvage radiation and are currently free of disease.

Because of the significant rate of upgrading and upstaging in our patient population, we explored the subset of patients using more stringent criteria. Therefore, from the 66 patients above who underwent an immediate postbiopsy radical prostatectomy, we identified 29 patients who had a preoperative Gleason sum of 6 or less, PSA less than 10 ng/dL, percent cancer in specimen < 20%, and a PSA density < 0.15 ng/mL^2. On review of the prostatectomy pathology, these patients behaved similarly in regards to upgrading with a rate of 62.1%. This included five patients (17.2%) who had Gleason 8-10 on final pathology and 13 patients (44.8%) who had Gleason 7 disease. However, none of these patients had any upstaging to T3 disease or higher. Details are shown in Table 5.

Discussion

With the advent of the PSA, active surveillance has become a popular treatment strategy for low stage and low grade prostate cancer. However, questions remain as to the safety of this management strategy. Previous studies including the Surveillance, Epidemiology, and End Results (SEER) Medicare data have shown that active treatment results in a survival advantage over observation in low to intermediate disease. However, this study was observational, non-randomized, and the possibility of selection bias in the two cohorts exists.[7]

Other studies have shown no increase in prostate cancer specific mortality with active surveillance. Klotz found that in 299 men, 34% had evidence of disease progression but only 0.8% had died at 8 years. Also, a majority of the original patients were still on active surveillance and had not undergone definitive therapies.[5] It has also been shown that a delay in surgery in a similar patient population does not alter prostate cancer curability. This was seen in 38 patients who underwent a delayed radical prostatectomy at a median of 26.5 months. There was no statistically significant difference in pathology between this group and the 150 similar patients who underwent immediate surgery.[8]

Percentages of men on active surveillance protocols vary between different studies. According to the CaPSURE database, between 1999 and 2004, 1886 patients met the Epstein surveillance criteria. However, only 28 (9.0%) patients ultimately went on an active surveillance protocol.[9] This is different from the Swedish prostate cancer registry which reports a 26% rate of active surveillance.[10] Another group which reports their rate of active surveillance is the University of California at San Francisco, where

TABLE 5. **Radical prostatectomy pathology (Gleason sum 6, PSA < 10 ng/dL, percent cancer in specimen < 20%, PSA density ≤ 0.15 ng/mL²) 29 patients**

Gleason	Gleason sum 5-6 11 (37.9%)	Gleason sum 7 13 (44.8%)	Gleason sum 8-10 5 (17.2%)
Stage	T2 29 (100%)	T3 0 (0%)	
Margin status	Positive 6 (20.7%)	Negative 23 (79.3%)	
Lymph node status	Number of patients undergoing LAD 25 (86.2%)	Number of nodes mean/median/range 6.1/5/0-19	Number of positive nodes 0
Percentage of tissue involved with cancer	Mean 6.8	Median 5	Range 1-40

they report a dramatic increase in enrollment within the last few years. In fact, they report that they have enrolled 91 men in just the first half of 2007.[11] In the future, studies such as the PIVOT and PROTECT trials will give us additional data on the safety and efficacy of an active surveillance protocol. These trials are randomized, prospective studies which will compare expectant management to radiation therapy and radical prostatectomy.

Although most clinicians will agree that patients with low risk features on prostate biopsy are good candidates for active surveillance, the dilemma in management rests with the risk of progression and/or risk of missed high grade cancer on biopsy. Berglund et al from Memorial Sloan Kettering recently published their data on repeat biopsies of patients who were initially eligible for their active surveillance protocol. They found that 27% of the 104 patients had upstaging or upgrading and concluded that immediate repeat biopsy may be prudent for those on active surveillance.[12] Another group followed 186 men prospectively on an active surveillance protocol. Ninety-two men underwent repeat biopsy with 34 (36%) demonstrating disease progression on re-biopsy.[13] Recently, Conti et al reported their data on active surveillance. Of the men who met their criteria, they identified 236 men who underwent radical prostatectomy. They found that 35% had Gleason upgrade, 11% had extracapsular extension and 2% had seminal vesicle involvement.[14]

Although many studies show that active surveillance for prostate cancer is safe and an effective treatment strategy, this report demonstrates an alarming 65.2% of upgrading and upstaging on final pathology in those that chose immediate radical prostatectomy. One possible explanation is that our veteran population is a different demographic than the community population. An example of the disparity in prostate cancer outcomes is seen in the CaPSURE data. One study found that the veteran population had on average; lower income, less education, and more comorbidity at presentation. They were also found to have higher risk prostate cancer and a decreased likelihood of undergoing definitive therapy.[15] However, a potential benefit is that theoretically, most barriers to access care are removed in this population.

Recently, another possible explanation for the veteran population being different from the community population is Agent Orange exposure. As the Vietnam War veteran population is increasingly being diagnosed with prostate cancer, there seems to be an anecdotally larger percentage of men with high risk disease. Chamie et al found a significantly higher rate of prostate cancer in those exposed to Agent Orange than those who had not been exposed. Also, the exposed group was found to be younger at diagnosis, have a higher rate of Gleason 8 to 10, and was more likely to be found with metastatic disease at presentation.[16] Kane et al also found Agent Orange to be a significant factor on multivariate analysis when predicting for upgrading/upstaging in prostate cancer.[17] Although we do not have data on Agent Orange exposure in our study population, this is brought up as a possible confounding factor.

The rate of patients continuing on active surveillance protocols in any population remains variable. Klotz et al report their experience with a relatively large cohort of 450 patients. They found that at 2, 5, and 10 years the probability of a patient remaining on active surveillance was 84%, 72%, and 62%, respectively.[18] In another cohort of patients, 82 of the 500 patients enrolled in an active surveillance protocol underwent

definitive therapy; 83% due to study protocol while 17% was secondary to patient anxiety or other reasons. In this same study, they reported that of the 170 men who had at least 1.25 years of follow up, 24 (14%) did not comply with their 1 year repeat prostate biopsy.[19] In our patient population, we found that only 24/45 (53.3%) of patients complied with the 1 year prostate biopsy. Possible explanations for decreased compliance in our cohort could include the large distance that patients must travel to be seen at our VA, socioeconomic factors, and poor counseling about the active surveillance protocol. Again however, potential barriers to care such as insurance largely do not play a role in this population and raise serious concerns about the use of "active" surveillance in this population.

There are several limitations to our study. Implicit in any active surveillance protocol is the willingness and ability of the patient population to follow up and comply with the protocol set forth by the treatment team. Several factors may contribute to a patients' non-compliance. Although systems are in place to insure timely scheduling, often times appointments are missed secondary to lack of transportation, decreased financial resources, and lower education and health literacy. At the KCVA, several systems are put into place to help bridge the gap. Among them are phone calls to patients prior to appointments, a printed list of upcoming appointments at each visit to the hospital, a printed list of all active medications at each visit to the hospital, and reminders by the health care team about their upcoming procedures. Many of these systems have been put into place recently and may aid in our patients' compliance with our active surveillance protocol in the future.

Second, our criterion for active surveillance does not correlate with any existing protocols. We chose to include patients with cancer in 20% or less of their total biopsy tissue based on the way our pathologists report on our specimens as described above. However, only 3 of the 61 patients had 20% of their biopsy tissue involved with cancer while the rest all had 15% and under. In our cohort of patients, the average tissue involved with cancer on TRUS guided biopsy was only 6.56%.

Another potential limitation of our study is that we used a PSA criterion of 20 ng/mL. Although this is in line with the Hardie selection criteria, most other protocols use a lower PSA. Three patients had a PSA above 10 ng/mL in our study. As mentioned previously, all of these patients had upgrading to primary or secondary Gleason score 5. These patients were included in our analysis as patients during that time frame would have been offered active surveillance. Furthermore, with our subset analysis using more stringent criteria for active surveillance, we still found a rate of upgrading at 62.1%.

One other possible limitation is the inconsistency of the pathology reading. Because the same pathologist is not reading the biopsy and the final prostate pathology, there may be some inter-observer variability. A study in which the same pathologist reads the biopsy and the final specimen may show decreased rates of upgrading.

Even with the above limitations, our data is concerning for a number of different reasons. The rate of upgrading at radical prostatectomy of 65% raises concerns about basing treatment decisions on a single initial biopsy. As described above, this may be a result of several factors including, biopsy technique, pathologic variabilities, or patient factors mentioned above. However, all of these factors mentioned are similar to most VA hospitals across the country. Furthermore, the 53% compliance rate with the active surveillance protocol is equally disturbing. All patients on an active surveillance protocol at the KCVA are reminded of their 1 year prostate biopsy at each follow up visit. And although they are typically compliant with their PSA blood draws, a large number of patients choose not to comply with the recommendations for repeat biopsy at 1 year. In addition, the rate of upgrading on those that chose to undergo repeat biopsy emphasizes the need for such monitoring. This questions the efficacy of an active surveillance protocol at our VA and may have serious ramifications of how we consider this form of therapy in the future.

Conclusion

The VA hospital, theoretically, represents a logical institution in which to offer active surveillance for patients with low risk prostate cancer. However, the safety of this lies in the ability to detect those with progression. In our patient population, we found that only 53.3% on our active surveillance protocol complied with the 1 year prostate biopsy. Furthermore, in patients who were candidates for AS but chose RRP as initial management, an upgrade and upstage rate of 65.2% was found. This has important implications for those contemplating an active surveillance protocol. Therefore, all patients need to be strongly encouraged to comply with their yearly TRUS biopsy as well as with all of their PSA tests in order to minimize the risk of undetected progression. Also, given the rates of undergrading, patients in this setting should be offered an immediate repeat biopsy prior to enrolling in an active surveillance protocol. □

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