Active Surveillance

Kristian Novakovic, MD

Co-director, NorthShore Active Surveillance Program

I. Watchful Waiting Versus Active Surveillance

"Watchful waiting" is an older term that basically refers to waiting to see what happens with the prostate cancer. Essentially there is no extensive monitoring of the disease that goes on, and if symptoms should occur, which are usually related to significant progression of the disease, those symptoms are managed in a palliative manner.

Active surveillance on the other hand is an entirely different strategy. Active surveillance involves careful monitoring of the cancer, and we have several ways of doing that including following the PSA and doing repeated biopsies. We use those things to determine if the cancer is changing rapidly or significantly. We then intervene with an attempt to cure. The key difference between active surveillance and watchful waiting is that if intervention is necessary with active surveillance, the intention is to cure.

II. Active Surveillance Pros and Cons

1. Pros

Many urologists and other healthcare professionals believe that screen-detected prostate cancers are both over diagnosed and over treated. Finding the cancer is one thing, but treating everyone that has prostate cancer may result in the over treating of some people thereby exposing them to potential complications of treatment that perhaps they didn't have to go through.

2. Cons

The cons of active surveillance include the possibility of the cancer progressing too far and the window of curability being lost and patient anxiety during active surveillance. There is also some morbidity with regard to repeat biopsies, as the active surveillance protocol includes intense monitoring. Finally, there is a theoretical risk of increased difficulty in performing a radical prostatectomy if there have been multiple biopsies though some of us don't think that is really a major concern.

III. Prostate Cancer Prevalence and Mortality

A newborn American male has about a 16% lifetime risk of being diagnosed with prostate cancer, and there is a new case of prostate cancer diagnosed every three minutes. About one-third of men over the age of 60 and one-half of men over the age of 70 have prostate cancer, but the lifetime risk of death from prostate cancer is only about 3%, a major difference. A lot of men are diagnosed, but not that many are going to die. That

being said, prostate cancer is still the second leading cause of cancer-related death just behind lung cancer.

IV. Prostate Cancer Screening Trials

In terms of diagnosing prostate cancer, there is a test called the PSA (Prostate Specific Antigen), and we look for changes in the PSA or elevation in the PSA. Recently, however, a couple of major trials have asked whether screening for prostate cancer saves lives and whether it makes a difference in terms of deaths from prostate cancer. Both trials were published in the *New England Journal of Medicine.*

1. American Trial

The American Trial consisted of about 76,000 men randomized to either annual screening or what was called "usual care". After roughly 10 years of follow up, the death rate from prostate cancer was very low in both groups and did not differ significantly between the two groups.

2. European Trial

The European Trial consisted of approximately 160,000 men who were randomized to annual screening or no screening at all, and after the first 10 years of follow up the risk of death from prostate cancer was the same between the screened and unscreened groups. After 10 years, there was a 20% reduction in the risk of death in the screened group, which was a significant difference.

Both trials did point out that in order to save somebody from dying from prostate cancer, one has to screen a large number of men. In the European trial, at eight years about 1,400 men had to be screened, and 48 men had to be treated in order to prevent one prostate cancer-related death. As we go out further in the study, the number needed to treat in terms of patients is going to go way down. There is likely to be a benefit, but you are going out 15 years from the initiation of the screening and at the age of 65 median life expectancy is only 14 years. Could you live with the disease versus having to treat it and really not change the outcome in terms of the length of life lived?

V. Biochemical Recurrence Rates and Recovery of Urinary and Erectile Function at One Year Following Radical Prostatectomy

All prostate cancer treatments regardless of what they are can be successful in treating prostate cancer. We know we can treat prostate cancer and in many cases cure it, but there are some complications. The Trifecta that we look for in treating prostate cancer is cancer control, maintenance of continence, and maintenance of erection. According to the data, however, getting the Trifecta doesn't happen all of the time, and that applies to surgery as well as radiation and other treatments. Despite this, I do want to point out that there is some data that treating prostate cancers improves survival relative to not treating them.

VI. Randomized Trial of Watchful Waiting Versus Radical Prostatectomy

A Scandinavian trial was published of 695 men that found an absolute risk reduction of 6.1% in prostate cancer deaths at 15 years in men undergoing radical prostatectomy versus watchful waiting. The number needed to treat to prevent one prostate cancer death was fifteen. One of the key take-aways from the study was that the benefit was really only significant in men under 65 years-of-age. Patients who are older who have low-risk disease may be able to be treated with active surveillance very successfully. It may not be the best option for younger patients, and the data speaks to the fact that there is a significant improvement in terms of prostate cancer death in patients who undergo treatment, younger patients in particular. Even in the low-risk group there was some benefit in terms of a 4.2% reduction. The option of active surveillance for the appropriately selected patient should be offered.

VII. NorthShore University Health System Active Surveillance Clinical Trial

1. Eligibility Criteria

In terms of the NorthShore active surveillance clinical trial, we want patients whose age is over 60. They have to have a clinical stage of T1c, meaning the cancer was detected only by PSA and not by palpation or a T2a where the disease is palpable in a very small area of the prostate. The biopsy Gleason score can be six or less, and in terms of the diagnosis of prostate cancer we need a 12-core biopsy with no more than 3 of those cores being positive. The maximum tumor length can be no more than 50% of any one core, and the total volume of cancer has to be less than 5% of the biopsy volume. These are very strict criteria for active surveillance. In addition, we require men as they enter the protocol to undergo a repeat confirmatory biopsy. So within six months of their initial biopsy or entry into the protocol we want them to undergo a second biopsy at which time we use a 3-dimensional ultrasound imaging machine that allows us to biopsy certain parts of the prostate that are a little bit more difficult to get at and do that as accurately as possible. We want to confirm that we do have what we consider low-risk prostate cancer before we allow patients to continue on the protocol.

2. Protocol Schedule

Once patients are in the protocol, they are followed with PSA tests every three months. We check testosterone levels and PC83 levels, a urine-based marker for prostate cancer. Currently, the protocol requires biopsies every two years after the confirmatory biopsy. However, if there were a concern with regard to a change in the PSA, we would recommend an earlier biopsy. We also follow a number of research questionnaires, which are really focused on quality of life. The protocol is not only designed to manage prostate cancer itself, but it is also designed to address global health.

3. Current Snapshot

We have considered 152 patients for enrollment, but we have only entered about 100 into the trial. There are a significant number of patients who are not entered, and that is

because we don't recommend that they get into it either because they are too young, or their disease characteristics don't qualify them for the trial. We urge those patients to get treated and not participate in active surveillance.

VIII. Active Surveillance Clinical Outcomes

There are several major studies that are currently following patients on active surveillance. There are quite a few patients enrolled, and there is a reasonable amount of follow up. The number of patients that are treated is not insignificant, but our intent is not to force patients to stay on active surveillance forever. It is to allow them to use that option if it is still in their best interest. Out of all of the groups in 2010, two deaths were reported, and two had metastatic disease. Overall survival is quite high. At least with the level of follow up that is utilized in the trials, patients are doing quite well on active surveillance.

IX. Risk Stratification

1. Cumulative Incidence of Disease Progression at Initial Surveillance Biopsy

A major concern about the idea of active surveillance is whether we can really risk stratify, and we do have some indicator of what is going to happen in the future. The Hopkins group published on their follow up of patients on active surveillance. In terms of the risk for progression in patients who had disease progression at their initial surveillance biopsy, if their percent free PSA is greater than 15 and there is less than 35% involvement of any one core, the risk of progression is only 7.6%. On the other hand, if the serum free PSA is less than 15 and there is more than 35% involvement of any one core, the risk of progression is about 30%, which is significant.

2. Cumulative Incidence of Disease Progression Three Years After Initial Surveillance Biopsy

Looking at the risk of progression three years after the initial surveillance biopsy, with a PSA density of less than 0.08 and a negative surveillance biopsy, the risk of progression is only 11%. However, if the density is greater than 0.08 and there is a positive surveillance biopsy, the risk is 53.6%.

In the NorthShore protocol, of the patients who come in with a diagnosis of prostate cancer who undergo a confirmatory biopsy, about 50% of them have had negative biopsies. That means not that they don't have prostate cancer, but that they have a low volume of cancer at present and are good candidates for the protocol as long as their initial biopsy sample qualified them and the follow-up biopsy confirms that initial finding or is negative, which it has been in many cases. Those patients are good candidates for active surveillance.

X. Pathological Outcomes

1. Men in Whom Active Surveillance Fails

What happens in patients who fail active surveillance and undergo treatment for progression of some sort? About 65% of those men in the study had organ-confined

disease. Extracapsular tumor extension was present in 35%, positive surgical margins in 15%, seminal vesicle involvement in 2% and lymph node involvement in 4%. Other than the organ-confined disease, the others are concerning in terms of the potential for the cancer to be more severe and progress. What we do know also is that in the Duffield publication, the men who were in active surveillance that failed were failing after one to two years in the active surveillance follow up. We think those patients had a cancer that was under sampled and was more significant at the time of their entry than was initially thought. In most cases, prostate cancer grows very slowly. The other concern we are trying to address with our three-dimensional ultrasound is that finding cancers that are anteriorly located in the prostate is a little bit more difficult. Again, the concept of under sampling comes up. All of this underscores the need to be very careful about patients who are entered into active surveillance, and that is why we are so vigilant about watching them and doing things like repeat biopsies. We don't want to miss the cancers that need to be addressed.

2. Is active surveillance, delayed radical prostatectomy, associated with a higher risk of unfavorable outcomes?

Looking at patients who undergo immediate treatment versus delayed treatment, really there isn't a difference at least in the publication by Van den Bergh in *Cancer*. The Gleason scores were essentially the same. In terms of capsular penetration, there was no significant difference. As far as positive margins, there was no significant difference, and tumor volumes were essentially the same. Follow ups were similar as well. The bottom line is there is a lot of data out there to suggest that if you do undergo active surveillance and then decide to come off of it, you are unlikely to have lost the window of opportunity for cure. We still are going to be able to treat your cancer and in most cases cure it.

XI. Conclusions

Active surveillance is different from watchful waiting. It's not the same thing. You're not just going to let the cancer do what it's going to do. We're going to watch it, and then we're going to intervene if that is needed. We are trying to avoid overtreatment and morbidity of treatment. In terms of the clinical outcomes, they are generally favorable, but again it really speaks to how the stringent criteria. I personally believe that the criteria have to be very strict. We don't just want to watch everyone with active surveillance; we want to pick those patients that are appropriate for it. We can risk stratify patients and determine based on their initial biopsy and surveillance biopsies if there is a reason to come off active surveillance to undergo treatment or if it's appropriate for them to stay on active surveillance. We can use some of the criteria that are out there to determine that. In terms of pathological outcomes, they are really similar in terms of immediate versus later treatment, and for appropriately selected men active surveillance is an option. Again, with regard to the quality of life issues and dealing with that element of active surveillance, the anxiety of having the cancer and how to do it, the onus is on physicians to help you deal with that and it has to be dealt with appropriately.

XII. Questions

Participant

One of the things that we see happening in the community practices in many cases is that the compensation for active surveillance management is not anywhere near the compensation for other therapies. How can a patient be aware of that situation, and how can they manage it to their own benefit?

Kristian Novakovic, MD

That is difficult because there is a self-interest involved for the physician. There is recent data to suggest that if you are doing active surveillance on patients, you are seeing them fairly frequently. They do undergo repeat procedures, and they are going to get comprehensive urologic care. There is data to suggest that having patients on long-term active surveillance is actually beneficial to the physician. There is controversy around that. There isn't a billing code for it, but really simplistically if you treat someone that is where your income is. It isn't from seeing patients in the office for 15 minutes to a half-hour at a time. The word on active surveillance needs to get out to patients in terms of being an option for them to consider. As long as patients are educated about it, many times they will go to the physician with the information. Then the physician and patient can sit down, have a conversation and make an informed decision together about what to do.

Participant

Given all of the options that exist, how many opinions should a patient get before making a decision?

Kristian Novakovic, MD

It comes down to what a patient is looking for. If I think that a patient has a cancer that really needs to be treated, I will try to push them in that direction because I think that is my responsibility. A patient has to develop a bond of trust with his physician. If he is able to do that and feels like the physician is treating him and communicating with him the way he would like that is really when the decision can be made regarding moving toward treatment.

Participant

Is it reasonable to counsel a 50-year-old patient with a family history of prostate cancer who has a PSA of 2.4 to wait and re-check his PSA in four months before making a decision on treatment?

Kristian Novakovic, MD

The window of curability would not be lost in that situation if a patient were to recheck his PSA in four months given the natural history of prostate cancer even in a 50-year-old. There is no level of PSA below which a patient has no risk of prostate cancer. My typical practice would be to repeat the PSA in that situation, and if it came back at less than one,

I would continue to watch. If it came back the second time in the 2.4 range, I may suggest that he undergo a biopsy.