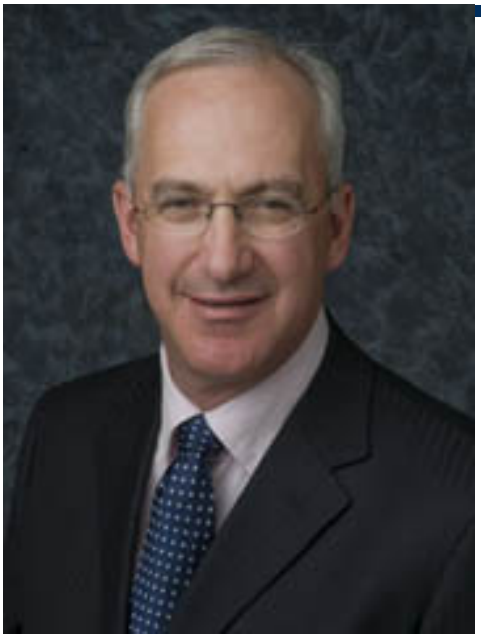
Active Surveillance: Q&A with Dr. Laurence Klotz



Sunnybrook Health Sciences Centre's Laurence Klotz, MD, speaks with PCRI about management of low-risk prostate cancer with Active Surveillance.

What is active surveillance, and how does it compare with other methods of treating prostate cancer?

The concept of conservative management for prostate cancer is not new. In fact, in Scandinavia and England in the 70s, basically no one was treated until they had metastatic disease. And the idea was that treatment didn't really have much effect; this was a slow-growing disease and people didn't die from it. We now know that is wrong in many respects, and so the idea of no treatment has pretty much been abandoned.

When PSA emerged around 1989, and suddenly all this early prostate cancer was being diagnosed, the idea was that many of these patients harbored aggressive disease and should be treated radically. And virtually all newly diagnosed men in the United States, Canada and most of the Western world were offered aggressive treatments for their disease.

But not everyone with prostate cancer is destined to die from it, and the real problem with PSA screening that should be addressed is the over-diagnosis of clinically insignificant disease.

The crux of the problem is that the likelihood of harboring small bits of prostate cancer in a man is about equal to his age as a percentage. So that means in men who are, say, between 50 and 70 - which is the key age group for diagnosing and treating prostate cancer - somewhere around 60 percent will have small bits of prostate cancer. And many of them will have an elevated PSA, due, for example, to benign prostatic enlargement. This leads to a biopsy, and the biopsy finds these little bits of prostate cancer. And these patients were all getting radical treatment, even though what they had was (in my view) really part of the aging process, something that develops more or less normally in men with age.

The active surveillance was an attempt to grapple with this by saying, okay, we know that guys who have bad prostate cancer need treatment, and benefit from it. And that's been clearly shown in randomized trials. But the patients dying of prostate cancer tend to have higher grade (Gleason) cancer. So maybe we can take the ones who have low-grade cancer, just manage them conservatively, and keep a close eye on them because some may develop something worse. We can then treat those who get reclassified as having higher risk disease, and observe the rest.

So we started doing that around 1996, more than 15 years ago. At the time, it was considered very experimental, and patients had to sign an informed consent form that they were going on a clinical trial. Yet patients flocked to this approach, because word was getting out that there were problems with the outcome of surgery and radiation in terms of quality of life.

CONTINUED ON PAGE 12

And so, cycle forward about 15 years, there's now about 4,000 men reported in the world literature that have been followed prospectively this way, and hardly anyone dies of prostate cancer (in the range of 1 percent).

The vast majority of men who are found to have these little bits of low-grade cancer have absolutely no threat to their life, and can be managed with conservative treatment. **A few of them, however, harbor worse disease. It's just missed on the biopsies, so the biopsy needle just gets a glancing blow off the edge of a large cancer, and it shows up as a small amount of low-grade disease.** So you have to repeat the biopsy once in a while, you have to follow the PSA, and there's other techniques like **multiparametric MRI** that may come into play.

But the basic concept is that most of these men don't have a real disease at all – they have something that's a normal part of the aging process, and doesn't need to be treated. That's now very robust I would say, and most people accept this. It's been a tremendous boon to men to give them the opportunity to avoid the side effects of treatment.

What makes a patient a good candidate for active surveillance?

The main candidates for active surveillance, the patients for whom there is very little controversy, are guys who have **a mildly elevated PSA, preferably less than 10**, and whose biopsy shows **relatively small amount of Gleason 6 prostate cancer.**

What do you recommend for men going on an active surveillance program, as far as self-care?

We know that a diet that is good for your heart and that's good for your prostate is the same diet. So I advise men to watch their weight, avoid too much animal fat and red meat, and reduce caloric intake to some degree. And for the men who want to be proactive, I think it's reasonable to be on some micronutrients, like lycopene, vitamin D, and perhaps a statin.

How do you monitor for progression?

Patients need to have a second biopsy, and we usually wait around 9 to 12 months to do that. The reason to wait is mainly to give them a break, because most men aren't too thrilled with the idea of another biopsy.

We monitor the PSA every three months for the first two years, and then every six months. Although the PSA is not reliable as a trigger for intervention, it is a guide.

For example, in our series, the patients who did badly all had a very rapid rise in PSA. The problem is, so did a lot of other guys that did perfectly well. So it is a flag, but not a trigger. They have the biopsy within a year, which targets the areas that tend to get missed on the first biopsy, and that's very important.

In a normal transrectal diagnostic biopsy, the anterior (the front part of the prostate) doesn't get evaluated very well, which is not usually a problem because most cancers aren't in that area.

But in the surveillance population, a few of them do have these large anterior cancers. So the confirmatory biopsy targets the area of the prostate that tends to get missed in the initial biopsy. And if that's negative, or shows the same thing, then the frequency really falls off and we biopsy the patients around every four years. And when they reach age 80, we stop.

CONTINUED ON PAGE 13

The multiparametric MRI has emerged recently as a very powerful tool in managing patients on surveillance. We don't do it with everyone. But if a patient has a significant increase in the volume of Gleason 6 cancer on their repeat biopsy, or what looks like worrisome PSA kinetics, or if there's Gleason 3 plus a small amount of 4 and the question is 'how much disease does the patient have?' the MRI is very useful. So that's our basic monitoring strategy.

What are your current research interests?

In the lab, we're interested in a micronutrient called capsaicin. This is the micronutrient that is found in hot chili peppers.

The interesting thing about capsaicin is that there's a specific receptor in prostate cells for capsaicin, which is called TRPV-6. When activated, that receptor seems to induce very positive effects, and it inhibits the proliferation of cells and invasion. There aren't many micronutrients that actually have a specific receptor, and it's also increased in advanced prostate cancer compared to benign, and so on.

In the lab, capsaicin actually works very well in mice. If you grow prostate cancer in a mouse, capsaicin basically causes arrest of growth. Whether it is going to work in humans is still something that we are exploring. In patients who are very interested in being proactive about taking micronutrients, it may be worthwhile (and, by the way, it is available in pill form and does not burn either going in or coming out, unlike the real version in the hot chili peppers!).

The other project that your readers might find interesting is a new treatment for prostate cancer that we've been working on for about the last 10 years, in collaboration with a biophysicist named Rajiv Chopra.

Essentially, this treatment is a form of thermal ablation of the prostate. It uses ultrasound energy, delivered by a transducer to heat prostate tissue. The ultrasound waves are converted to heat in tissue, and cells do not tolerate an increase in temperature beyond about 55 degrees Centigrade, which is about 120 Fahrenheit. It's lethal to cells.

So, there are many ways to direct ultrasound energy. In fact, there is a technique which has been used for quite some time called high-intensity focus ultrasound (HIFU), which uses a transrectal probe to direct the energy at the prostate, heat it and kill it. The disadvantage of that approach is related to precision, because there's no way to measure directly what temperature the tissue is reaching. (It is also not approved in the U.S.)

But it turns out that MRI can give a real-time thermal map of tissue. It's really quite amazing: put a patient in an MRI scanner, and you can see what the temperature is in all of the tissues in the body that you're imaging. Now, you can imagine if you're using a treatment that works by heating tissue, that's very powerful in terms of knowing what you're doing.

The approach that we use is transurethral ultrasound transducer. It's about the same diameter as a foley catheter. It has a series of ultrasound transducers on it, each one is about 5mm long, and this is put into the patient, and then he's rolled into the MRI and imaged.

The ultrasound transducers are turned on, they start to heat the tissue, and the thermal map of the tissue then automatically feeds back to control how much energy is delivered.

CONTINUED ON PAGE 14

You can heat to the target temperature of 55 degrees with tremendous precision. You can ablate the whole prostate in about half an hour. And the distance from ablated to normal tissue is only about 2mm. So we've reached a point where we started doing this in humans about two years ago, and we're still kind of in the "proof of principle" stage.

In the study we're doing now, we take men who are going for surgery, (usually radical prostatectomy for high-grade cancer), we do an MRI, target the cancer, and then immediately before the surgery, we go back to the MRI unit with the patient having a spinal anesthetic and we ablate the cancer with this technique.

Once we're set up to do it, it takes about 15 minutes. It's a form of focal ablation treating maybe a third of the prostate. And then the patient is taken out of the MRI, goes into the operating room, and we see if we actually killed off the cancer we targeted.

We're going to be finished with this phase in about six months I expect, and hopefully we will show that yes, you can target the cancer, treat it effectively using this technique, leaving the remainder of the prostate un-treated, because you're only treating this index target.

And then, we hope, we're going to begin to treat patients with this as a primary therapy. So it's been a long series of technological developments, and we're just at the point where we think this is going to be available to patients. ◆

NOTE:

The National Institute of Health defines the difference between Active Surveillance and Watchful Waiting as such:

"Active Surveillance is a disease management strategy that delays curative treatment until it is warranted based on defined indicators of disease progression.

In contrast, Watchful Waiting is a disease management strategy that forgoes curative treatment and initiates intervention only when symptoms arise."

For more information, please visit

http://consensus.nih.gov/2011/docs/prostate/Final%20Statement.pdf