Active Surveillance in Prostate Cancer

One in seven men will be diagnosed with prostate cancer in his lifetime and the likelihood of being diagnosed increases with age. In this show, Active Surveillance expert Dr.

Laurence Klotz discusses the value of Active Surveillance as a management strategy to reduce over treatment of the disease for men diagnosed with low-risk prostate cancer.

Full Transcript:

Priya : Good evening and welcome to the Cure Panel Talk Show. I am Priya Menon, Scientific Media Editor at CureTalk, Cure Panel Talk Show, and I welcome all of you for a discussion on prostate cancer. All Cure Panel shows on prostate cancer are conducted in association with Prostate Cancer International and the Prostate Cancer Foundation. This is the fifth time we are discussing prostate cancer on the Cure Panel platform. On our previous episode, we discussed focal therapy and HIFU with Prof. Mark Emberton of University College of London Hospital. Today, we have with us a very distinguished guest, Dr. Laurence Klotz. Dr. Klotz is a very well known and highly regarded specialist in prostate cancer management and a Professor of Urology at Sunnybrook Health Sciences Centre, Toronto, Canada. Welcome to the show, Dr. Klotz.

My co-host for the show is Michael E Scott. Mike is Co-founder and President of Prostate Cancer International, a prostate cancer-specific, not-for-profit educational and informational organization based in Virginia. Supporting Dr. Klotz and Mike on the panel are experienced and knowledgeable prostate cancer survivors and advocates, Tony Crispino, Walter Green, and Thomas Kirk. I extend a hearty welcome to all panelists and to all our listeners.

Today, we are discussing active surveillance for management of low-risk prostate cancer. Prostate cancer is the second most common cancer in men in the United States. An estimated one in seven men will be diagnosed with prostate cancer in his lifetime and the likelihood of being diagnosed increases with age. The American Cancer Society estimates that about 223,000 new cases of prostate cancer will be diagnosed in 2014. For years, doctors have debated the merits of active surveillance. Active surveillance for low-risk prostate cancer is an attempt to reduce the overtreatment of the disease. The approach involves initial expectant management rather than immediate therapy. Curative treatment is deferred while the patient is monitored and offered for evidence of risk reclassification to a more aggressive form of the disease. A recent study published in the March 6th edition of the New England Journal of Medicine reporting that the watchful waiting strategy, which is operating only after cancer spreads generally increases risks, has the debate over prostate cancer treatment flaring again. Let us learn and understand active surveillance from our expert and panelists. With that, I now hand over to Mike. Mike, you are on air.

Mike : Thank you, Priya. Good evening, Dr. Klotz. Is that okay? So, perhaps you could begin by giving us an overview of some of the things you think are important today in the development and management of a sound active surveillance practice.

Dr. Klotz: Well, perhaps to put it in the context, let me just begin with kind of the big picture, which is the problem of overdiagnosis in medicine in general and its become apparent, I would say, over the last decade or so that throughout medicine, whether its the management of hypertension, hypercholesterolemia, high cholesterol, osteoporosis, diabetes, well-meaning attempts to find diseases that are potentially serious earlier and initiate treatment earlier, all of which have the intent of improving the health of patients, have an unintended consequence of finding a lot of disease that is not clinically significant and would never have been discovered in the absence of these kinds of efforts to find earlier disease, so we call that overdiagnosis and these diseases which would never have caused a problem for the patient during their lifetime are referred to as clinically insignificant. So, there are many, many examples. Its really a malady of modern medicine in the sense that attempted earlier diagnosis consistently result in many, many people being diagnosed with diseases that they otherwise wouldn't know about and of course that risks overtreatment because once you are diagnosed with high blood pressure, diabetes, osteoporosis and so on, the tendency is to treat. So, there's an increasing recognition of this across the whole field of medicine and in the field of oncology or cancer in particular, there are many examples where this occurs, not just prostate cancer, although its one of the most important, but breast cancer, thyroid cancer, even lung cancer, normally a very disease has this probable diagnosis. Its particularly an issue in prostate cancer because we have very good evidence based on autopsy series. So, this is a situation where men who are dying of an unrelated cause had their prostate carefully examined and the likelihood of having small bits of low-grade prostate cancer is about equal to your age of the percentage. If you are 50, you have about a 50% chance of having these small bits of low-grade prostate cancer and in the majority of cases, they are not significant. You would go on to… Most men who have this eventually die of something else and never know they had it.

With the advent of attempted early detection driven by very reasonable concerns about finding cancer earlier when its more curable and more likely to be eradicated by treatment, as a result a lot of men conducted a biopsy that showed these little bits of low-grade prostate cancer. I refer to this as part of the… These small lesions are the small areas that are part of the aging process because they develop in almost all men with time and they are not a real disease, but they look like a cancer to the pathologist. They are called cancer and the result is once a man hears he has cancer, his natural reaction is to say, "This is terrible and I have to do something, you know, take it out, radiate it, get rid of it" and the result is that a great deal of clinically insignificant disease gets treated aggressively. Even that would be perhaps a perfectly acceptable situation if the treatment were innocuous. So, for example, if the treatment was a pill like a low-dose aspirin, it wouldn't really matter if patients were overtreated because they wouldn't have a lot of adverse effects in the treatment.

The difficulty with prostate cancer is that the treatments do have effects on quality of life that can be lifelong and can be quite substantial, and those side effects are perfectly acceptable if you have a life-threatening disease. I think most men would be prepared to, for example, sacrifice their erectile function if the alternative of dying of prostate cancer in a short time frame, you know, life to ball tradeoff, but if you are talking about a disease that does not pose a threat, it's a different story and that led to this approach where we said, "Look, we think we can identify the majority of these men who have had only what looks like the clinically insignificant cancer because their type of cancer has certain characteristics under the microscope of low grade. We think we can identify these men and rather than treating them straightaway, we watch them, we look for the ones who look like they have something worse over time using PSA and using other modern techniques and we treat those and we manage the rest conservatively and we started doing that in around 1996, now its like 18 years ago. At the time, this was considered extremely controversial. Many accusations were thrown around about how this is unethical, treating cancer, managing patients with cancer without any treatment and the patient will die unnecessarily, but I think reasoned one out and gradually there was an increasing acceptance. One of the reasons for this was that as experience has grown, it's become clear that this is quite a safe approach. It's still an approach in evolution where we are learning every year, we are learning how to do it better, but by now there are many thousands of patients managed this way around the

world with a long follow up and very good information about how this should be done properly. So, one of the striking changes, from my perspective, was how the pendulum has swung from really very much lack of acceptance by my colleagues who are committed to quite widespread acceptance all over the world. So, that's kind of an introduction to the whole area and I am kind of happy to discuss any aspect of this would you like it.

Mike: So, there's a pretty fundamental aspect to this that I noticed that you looked at a great deal to manage the question of whether and when any patients who have Gleason's 6 disease or at risk for metastasis. My understanding is that you believe that this is extremely rare and perhaps you would like to talk about that for little bit.

Dr. Klotz: Okay. So, let's just take a clinical scenario which is you have a 60-year-old male whose PSA has gone up and he goes on to have a biopsy and the biopsy shows there are a couple of positive cores. Typically the biopsy is somewhere between 10 and 14 needle sticks or cores, say two or three of those cores show some Gleason's 6 prostate cancer and I should just add for your listeners, the grading system or the way that the microscopic appearance of the cells is characterized is called the Gleason's score and for all intents and purposes, it goes from 6 to 8 for about 95% of patients. Six is considered low, eight is high, and seven is intermediate and I will come back with some of the details about that. But, Gleason's 6 is what we are talking about today, which is considered low-grade prostate cancer and most of the men who have the bits of prostate cancer develop normally with age, have morbid Gleason's 6. So, we now know that about a quarter of these patients have higher grade cancer somewhere in their prostate that's been missed on the initial biopsy and that is one of the major challenges of managing that on surveillance is to find those bad cancers early enough that they are still curable.

Another very small group have what you would call biological progression, which means over time, say over 10 or 20 years, that low-grade cancer progresses to higher-grade cancer. The best estimate is that that happens at the rate of about 1% per year, which means after 10 years, about 1 patient in 10 will have true biological progression from Gleason's 6 to 7 or higher and that leaves the rest, which is about two-thirds of patients, never have a problem and the question is how likely are those guys to have spread of the disease while you are watching them and we now have data, there's several studies. One involved 12,000 men with Gleason's 6 prostate cancer treated with surgery. Now, of course, the advantage of treating them with surgery is the prostate could be examined so you could exclude the possibility that they have higher-grade cancer that was hidden.

Another group, 14,000 men, who had lymph node dissection, none of the men in these series developed metastasis. A very few were described as having metastasis. The pathologist went back and re-reviewed their tissue and in every case found the evidence of higher-grade cancer. So, and I have had many, many groups around the world. Most practitioners like myself who typically look after thousands of patients, most of them have never seen a patient with true Gleason's 6 prostate cancer who has metastasis. They could be diagnosed with Gleason's 6 and have higher-grade cancer that metastasizes, but if its only Gleason's 6, they don't.

The second point on this area is that if you look at the molecular genetics of Gleason's 6 prostate cancer, by and large it lacks the molecular hallmarks of malignancy. So, we know now as a result of this revolution in molecular genetics, we know the molecular pathways that cells take when they metastasize or when they become cancerous. These are called the hallmarks of malignancy. Gleason's 6 by and large for tumor suppressor genes, oncogenes, growth regulatory genes, I don't want to get too technical, but for a whole series of these pathways, the genetics are normal whereas with higher-grade cancer they are abnormal. So, we have both molecular evidence and clinical evidence from huge series of long followup. Yet the risk of a true Gleason's 6 cancer metastasizing is either zero or very close to zero. I mean, its never going to be absolutely 100% because size and nature don't work that way, but the risk of that is very, very low. The major concern is to find the guys who are harboring higher-grade cancer and that's where some of the recent tests like MRI and biomarkers are increasingly playing a role, but my view and its not universally shared, but I would say increasingly widely shared, is that Gleason's 6 cancer does not fulfill the criteria for

a true cancer. It doesn't have the hallmarks of cancer, including the growing metastasizes.

Mike: So, let's talk a little bit about how you go about making sure that you are weeding out the patients who are high risk. One of the issues that is of concern to at least some in the patient community is that the idea of giving people annual biopsies is of itself providing risk for side effects of the time and, you know, I know a number of people have started thinking in terms of using multiparametric MRIs, using less frequent biopsies, but one of the problems I see at the moment is a lack of standardization across the urology community about how one actually practices active surveillance and so your views on that would be of great interest, I think, to people.

Dr. Klotz: So, first of all, no one with the exception of the group at John Hopkins who is really doing it for academic purposes, no one is really promoting annual biopsy. Our approach for a long time has been the following: The patient has the initial diagnostic biopsy and it tends to focus on the areas where cancers are most common, which is in the back part of the prostate, which we call the peripheral zone. We know that a lot of the patients have, when they have a hidden cancer, its in the front part of the prostrate, which is harder to reach from a transrectal approach. So, our view have been that you need to do what's called a confirmatory biopsy within a year. Some people do it within a few months. We wait about a year, give the patient a break, target the areas that are not targeted with the initial typical diagnostic biopsy that the front part of the prostrate, kind of outside, called the lateral prostrate. We target those areas with this confirmatory biopsy, and we find about two-thirds or three quarters of the patients who are harboring the bad disease with that confirmatory biopsy. Once that's done, our view is, okay, we have done a pretty good job of characterizing what this patient has, assuming that he isn't found to have anything more than Gleason's 6 cancer and after that we do it infrequently and the longer we have been at this, the less often we do the biopsies. Now for the typical patients, its every four to five years, until about age 80. So, we only do the biopsy in the patient who has had his initial confirmatory biopsy around every four to five years. The MRI is beginning to have a major impact here and the way we use it. So, i am in Canada where MRI is not as widely available as in the United States. We can't do the MRI on every single newly diagnosed patient, and actually my view is that's a perfectly reasonable idea. So, we do the MRIs only in those patients where either their repeat biopsy shows much more cancer than they had initially. We call it volume progression or their PSA kinetics looks bad, so the PSA is rising very rapidly or their repeat biopsy shows a little bit of higher-grade cancer Gleason's 7 cancer and they still want to stay on surveillance. So, we do the MRI selectively on those patients and it often will show, you know, large cancers and we will then biopsy that or treat the patient based on that.

So, I think going forward, your point is extremely correct that MRI has already started to replace the biopsy. We don't yet have their high-quality data to say, "Yes, its reliable." We know we can stop doing the biopsy if the MRI is negative, but that data is coming. We have one study from Memorial Sloan-Kettering that where the MRI was negative, 97% of the patients had no high-grade cancers. So, that's called the negative predictive value. The vast majority of the patients who have negative MRI didn't have any setbacks and that's a much higher percentage than we have had in the past. So, if that's borne out by further studies, I think, yes, the multiparametric MRI will begin to replace the biopsy and I completely agree with you that too many biopsies is a problem. Patients don't like it. It can cause erectile dysfunction and bleeding and other problems, so anything that can reduce the rate of the biopsy is appealing. Having said that, I do believe that the confirmatory biopsy that targets the parts of the prostate that tend to get missed initially is absolutely essential.

Mike: Dr. Klotz, is there any sort of working groups that's looking at starting to develop practice guidelines for active surveillance?

Dr. Klotz: Oh, so absolutely. There's a lot going on in the field and I should add by the way the approach we have taken has been adopted by quite a few other groups including the other largest group in the world that's called the [00:22:37] _____ Group which is based in Notterdam and they essentially do it exactly the way we do. So, just a couple of things. I mean there's an American initiative to develop a guideline. We have a Canadian initiative just coming out with a guideline in the next couple of months on surveillance and

we are trying to standardize this approach. There's also something called the Global Action Plan for active surveillance which is sponsored by the Movember Charitable Foundation, you know the mustache-growing foundation. I am sure you are familiar with that. So, the Global Action Plan for surveillance called the GAP3 program, amongst other things, is trying to develop a standardized approach act of surveillance. You know, I think most people who are doing this take a fairly similar approach whether the biopsy is done every, you know, three years or four years. This is, to some degree, a matter of personal preference, how anxious the patient is, how does he feel about having a biopsy, these are going to always be guidelines rather than hard and fast rule.

Mike: Sure. So, I would like to switch the conversation a little bit and talk about patient age because it seems to me there are two different basic strategies going on here. One is in the case of younger men, simply the idea that you are going to defer the need for treatment if it is needed for as long as possible. Then the other which is probably more relevant to all the men in the mid to late 60s or older, where you are definitely thinking about how can you avoid treating this person the full length of time. I would be interested in your views on the relative risks of using active surveillance in younger and older men. I think that's an important issue for people.

Dr. Klotz: Yeah. To my mind what you just said is one of the great misconceptions in this field. Keep in mind that, you know, 40% of men in their 40s have microscopic areas of prostate cancer and these can be found on the biopsy. The lifetime risk of dying of prostate cancer is somewhere around 2.5% to 3%. So, you have about, a man in his 40s has more than ten times greater chance of having low-grade prostate cancer than he does of dying of the disease and the second thing is that the vast majority of men who have Gleason's 6 prostate cancer never have any problems from it. So, I mean, I hear this a lot, you know the younger patients, they are eventually going to need treatment and this is simply not true. We know that based on plenty of experience with young men who were followed 15 to 20 years now, show no sign of having any problem. We know it just from the basic epidemiology, you can't have 10 times as many men having the disease have died from it and think that all of them are going to run into problem. So, as a general rule, being young does not preclude active surveillance. Now, there is an exception and that is that the majority of young men who are diagnosed with low-grade prostate cancer have only a small amount of cancer on their biopsy. There is a small minority whose prostate is loaded with low-grade prostate cancer and that's an unusual phenomenon and in my opinion those guys should be treated. If you have very extensive prostate cancer in your prostate in your 40s, even if its low grade, you may well have a problem and I think its completely reasonable to be treated, but that's the minority. That's a handful of patients.

The vast majority have very small volume disease, it really doesn't pose a threat. So, you know, I have no issue about offering surveillance to the vast majority of young men who were diagnosed and you know, the other side of the story is keep in mind the effects of treatment on erectile function, continence, and so on. For a 70-year-old to incur erectile dysfunction, the chances are he has got some to start with and we know from a number of studies that while older men still think about sex, it doesn't have the same urgency and importance for a lot of them that it does for younger men. So, the impact of treatment on the younger men is significantly greater and that's why, you know, I think surveillance is particularly attractive for younger men who are candidates and in the majority, its not need for treatment, it is the absence of treatment.

There may be some who, a minority, who progress over time and are treated when they are, say, 65 instead of 50 and because they have great progression for example and I think also those guys are ahead of the game because they have had an additional 15 years with normal erectile function with no problems with continence and so on and in the majority when it comes to treatment, even though it may have been delayed by 15 years, they still do well despite treatment having been deferred for so long. This is to emphasize a point that the prostate cancer mortality rate in men managed with surveillance in our series is very, very low. Very few people actually die of this disease, managed this way.

Mike: Thank you, Dr. Klotz. So, I think with this point, I am going to open this up to my other panelists and since we have Tom Kirk with us and he is responsible for running the world's largest prostate cancer support group and therefore hoping to try to educate as many of his men who are responsible, I would like

the view with Tom. Tom, do you have a question, couple of questions for Dr. Klotz?

Tom Kirk : Right. First of all, I thought this was very informative and as we find out more information from these studies, I think this becomes essential that we transmit this information to men with the disease. I thought the information was extremely positive and I think that that's part of what we need to share this information available, so I guess my question would be what are good solid ways that we can provide this current information that you are seeing very low death rates or mortality rates from men in this group, especially men with Gleason 6?

Dr. Klotz: Yeah. So… Just to clarify, you are kind of asking me how do you get the message out?

Tom Kirk : Yes, exactly.

Dr. Klotz: Yeah. So, you know, one of the challenges I have been dealing with for more than 15 years is the, what you could call the kind of, about the word cancer or the cultural perspective on this word. So, you know, and certainly when we started doing this, you know, I would say to a patient, "Look, you have cancer, but its not serious," and they would look at me, like, "What planet did you just arrive from? (laughter) You know, what are you talking about?" It was really incomprehension. Even then, I found that, you know, you start talking to patients about some of the facts that I mentioned and use words like pseudocancer, part of the aging process, a disease that half of men your age or two-thirds of men your age have and people can understand it quite readily and I should also maybe add that Toronto, where I live, which is a very multi-ethnic community, we have about 1,000 patients managed this way and they come from all over the world. Many of them don't have English as their first language. Many of them don't have much education and then at the other end, there are research scientists and physicians and so on who are part of this group. They can get it quite quickly, I think, and the other part of it is that my impression is that over the last, let's say, five years, there's been a lot more information in the lay media about overdiagnosis, about how not all cancers may be destined to kill you. The concept of surveillance has kind of gotten out there and there's a much greater acceptance by patients. I am not even talking about by the medical profession, but I think patients have some, a little bit of background now where this doesn't come as a complete shock to them that they have a malignancy that in fact is not life threatening at all and so I think its getting easier.

Now, how you go the next step which is to really kind of get that idea out there. That's, you know, a marketing challenge which is not really my area and I think that's where groups like your's come in and then they have a huge role to play at the support groups and when talking to the media and so on to get this message across that not all prostate cancer needs to be treated. So, I mean, I really value that kind of thing that your groups are doing in helping to promote that idea.

I might just add that one of the other phenomenon I have observed is I speak at these support groups periodically and, you know, typically the guy sitting in the support groups are men who have been radiated or had radical prostatectomy and maybe they have side effects and they are sitting, they are listening to me talk about how there is overtreatment and not all men need to be treated. This message doesn't naturally go over too well and sometimes the support groups are, there's a kind of emotional commitment to timely intervention, which is not wrong for the patient who needs it and let me just also emphasize, you know, I believe in treatment for prostate cancer. If a patient has higher-grade cancer, we have shown absolutely that treatment saves lives and I think we have made two mistakes. We have been too aggressive at the low risk and not aggressive enough at the high risk and so its all about kind of the balance of getting the thing right, so I am not in denial of this at all. I believe in treatment for prostate cancer but not for the low-grade type and you know, so the challenge is to get the support groups to come around to this idea and there certainly are some who are very supportive.

Mike: So, let's introduce our next panelist. Walt Green is an active surveillance patient. Walt lives in New York. Walt, you have a question for Dr. Klotz?

Walt Green: I don't have so much of a question, just to say that what Dr. Klotz had said is what Mr. Kirk

said, kind of tied together where getting the message out. I guess my only question to Dr. Klotz would be have you run into patients that couldn't win the mental aspect of this, in other words, they had the right numbers and they had the inclination to try active surveillance, but they just didn't have the mental ability to live with the thing that you mentioned, "You have cancer, but you are going to be okay." That type of thing. Have you run into that?

Dr. Klotz: Oh, for sure! So, I mean, we have some data about this. So, first of all, I can tell you its not that common. So, one of the major challenges for guys like me and my colleagues is the communication piece. Its to provide the reassurance with good information that will reassure patients. For most people, if you give them the right information, they are reassured and I have actually seen quite frequently, not mounting anxiety about having untreated cancer, but the opposite which is that a few years go by, nothing happens. They may know guys who have been treated, who have problems and they become ebullient. They become so appreciative of the fact that they have avoided the side effects of therapy that they are just deeply invested and committed to this idea of surveillance and even if some of them are upgraded, they say, "No, no one is touching me." (Laughter) So, its the opposite phenomenon.

So, in our series about 10% of patients who were treated who didn't have indications, but in most of them, in other words, they didn't have great progression or they didn't have any hard evidence that something bad was taking place, but most of them had a hint. So, you know, we have hard definitions for criteria for intervention. Most of the 10%, even their PSA was going up little faster than they were comfortable with even though it didn't meet our criteria which was a doubling time of less than three years or they had an increase in volume of low-grade cancer. Again, we didn't advocate treatment for just an increase in volume. So, they had a reason. One is just pure irrationality and in my opinion, there is about 5% of patients who just can't tolerate the idea of living with untreated cancer and these fall into two groups. One is patients who have pre-existing anxiety disorder and actually, you know, there's been some studies of these guys. They tend to be socially isolated, single, no kind of support infrastructure in their lives, you know they are loners, they don't have anyone to talk to about it and its tough for these guys and you can understand in their situation, you know, that they would be happier if they treat it. And then the second group is guys who are just very proactive about their lives. They tend to be, you know, leaders of industry, very type A individuals and you say, "You know, well, you can just watch." They say, "Doctor, I don't watch. My philosophy of life is to go for it and I am going for the treatment of this disease." And, you know, I respect that as well. I mean, because there's no risk-free strategy and they just have a kind of, their personality is such that they have to take action, but this is the minority and I would say for 95% of patients that thing you are describing which is these kind of anxiety of having untreated cancer is not a problem.

Mike: Umm.. So, our third panelist today is Tony Crispino who is running a support group, but he is also the prostate cancer patient advocate on the Southwest Oncology Group, so for all I know, he is going to ask you how to do clinical trials, but Tony, do you have a question for Dr. Klotz?

Tony Crispino : Yeah. I could start with clinical trials, but (laughter) I am going to come straight on over to asking what is really kind of the opposite question of what Tom Kirk just asked. Tom was mentioning about going on out to the patient community and getting the word out to them. My question comes back in the other direction. Pete Scardino, on Monday, came on out in the ASCO Post and stated that he perceived state-of-the-art right now for active surveillance being as much as have the patient diagnosed in the future, being on some sort of active surveillance protocol. My question is how we are going to get the medical community to come back on over and meet that expectation?

Dr. Klotz: Yeah. So, that's a long story, but let me just make a couple of comments. Its a very good question. First of all, I come to this from a Canadian perspective and for, I would say, a variety of reasons related to our very different healthcare system, active surveillance has been very widely embraced in Canada. My estimate is something like 75% of eligible patients, low-grade patients, in Canada are offered active surveillance. It may just be that urologists in Canada are fairly busy. They don't have to scrounge for patients. They have enough to do. It may just be our, I don't know, something to do with Canadian character, but its quite different. Most of the practice of medicine in Canada and US is similar. We have very

similar approaches despite our different healthcare systems, but this one thing different for active surveillance has been widely embraced. Its been very well embraced by many practitioners in the United States and its been rejected by a lot and I am aware of that.

There was a recent study that shows, I think in California, that of men being put on surveillance with low-grade cancer. Half of them were put on surveillance by only 3% of the urologists and about half or more urologists never offered it to a single patient. So, there's clearly a lot of drivers for this. There's fear of litigation. There is the desire to, you know, surgeons like to operate. The way I view this is I think that doctors in general want to do the right thing. They also want to be busy and make money, but they want to do it doing the right thing and there are very few of my colleagues who are so mercenary that they will subject their patient to the wrong thing just out of self-interest. I think that's a very rare phenomenon. But, there is though the gray zone and the gray zone is where, you know, there's a judgment. You could either manage the patient conservatively or not, both would be considered reasonable and under those circumstances since doctors are human beings, you know, their self-interest might come into it. So, my view is what the challenge is to shrink the gray zone, to get a broad acceptance that for most patients with low-grade prostate cancer, surveillance should be the therapy. If you are treating these people, its probably overtreatment and there is a better way and I think that message is getting out there and you know, I was asked for years. This urologist colleague would ask me, "Well, look, what happened? You know, you have a guy, you manage him conservatively. You are going to get sued."

And, you know, people worry about being sued. You can't avoid it completely. I think its only a matter of time before someone gets sued for overtreatment and you know, you are hearing about these things and to influence what is considered a normal clinical practice. So, I am optimistic that this is kind of a long-term project but that the profession is coming around and there are many examples where, you know, a Marxist would say, "Well, these guys are just acting out of self-interest." I don't believe that. There are many examples, not only in my field, in surgery in general, where surgeons have abandoned an operation despite the fact that it was a big part of their business when a better treatment came along or more effective treatment and I think that is happening in this field and will continue to happen.

Mike: So, at this point, Priya, I am going to hand this back to you because I know we have a number of questions from other people who may be on the phone.

Priya : Yes, thank you, Mike. This is for the audience. If you have a question for our panel or our expert, please press 1 on your keypad and we can bring you live on air to ask your question. Yeah. The person calling in from 916-375, you are live. Please ask your question.

Caller : Hi! My name is Jeff McClain, doctor and panelists. Being a former Canadian, I can like your program too. First question I have is on the loud is what supplements or diet do you think are helpful for a person with a low-grade prostate cancer?

Dr. Klotz: Yeah, that's a great question. So, the first thing I would say is that a heart-healthy diet and a prostate-healthy diet are basically the same diet. So and I think most people know what that is, you know, diet is low in animal fat, not too much red meat, lots of greens, fruits, vegetables. All the evidence we have is that if its good for your heart, its good for your prostate. We have very little evidence that modifying your diet is going to have any really significant effect on whether your prostate cancer progresses or not. That's a very hard thing to prove and so my view is how the diet that's healthy for your heart and if you are lucky it will have a beneficial effect on your prostate. I think avoiding obesity is important. There is evidence that physical activity is good not just for your cardiovascular system but also for your prostate. So, those are kind of the basic general recommendations I think everyone knows about, whether they adopt them or not is another story. What's that?

No, go ahead.

In terms of specific supplements, most of them unfortunately have not panned out. Vitamin E and selenium

look terrific. Based on animal data, based on epidemiologic data about populations that have lots of vitamin E and selenium in the diet, a very large scale study called the SELECT study was done and published about three years ago, that was a prostate cancer prevention trial using vitamin E and selenium, absolutely negative study. They didn't prevent anything. In fact, there was more prostate cancer with the vitamin E supplement than there was with the placebo and it was more diabetes with the selenium, so vitamin E and selenium both are off the map.

I will tell you what I would like the patients on, I am a believer in statins. So, a drug like Lipitor or pravastatin. I think for most men over the age of about 50, statins have some benefits. Now, this is again being a little bit proactive. The evidence is not that strong, but to my mind lower cholesterol is better. The second thing I think vitamin D. Particularly in northern climate like Canada, northern United States, vitamin D deficiency in older men is extremely common. There is evidence that vitamin D has a favorable effect on the prostate. So, I advise most patients to take a statin, to take vitamin D. Lycopene in the diet which is present in tomatoes. Tomatoes have to be cooked to get bioavailability, looks promising, but we don't have really solid evidence about it. Again, I think it is probably better to take it in the diet to take it in pill form.

But, finally, I have in my research laboratory, we are studying some of these micronutrients. The one that I find quite interesting is capsaicin, which is the active ingredient in hot chewing peppers, it makes them hot and capsaicin you can take it in pill form. It doesn't burn either going in or coming out, which is (laughter) a magic. Capsaicin looked quite promising in animals and in kind of tissue, in cell culture experiment and we are just doing some of the studies with capsaicin that looked promising, but we really don't have much in the way of human data and the other thing along the same line is metformin. Metformin is an old pill that's used for diabetes and there is a lot of evidence that metformin may reduce the risk of progression of prostate cancer and that study is also being done as we speak. In other words, men on surveillance put on metformin versus placebo, but you know, we don't have the data yet to really advocate that men on surveillance should be on those. They look promising. I think if you cannot go on anything, go on a statin, take vitamin D, take a multivitamin and that's about it. I am against expensive, kind of exotic micronutrients where we really have no evidences that they are doing much good.

Caller : Okay. I am allowed to ask a second question or shall I wait, Priya?

Mike: I think it would be nice if you could allow another person to ask the question.

Caller : I'll wait, I'll wait. Thank you, doctor.

Priya : Yeah. The caller calling in from (9176) 504-398, please ask your question.

Caller : Hi! I have a question for Dr. Klotz about the confirmatory biopsy that he described. Is this confirmatory biopsy done in the same manner as the typical transrectal biopsy with, let's say, 12 to 14 cores or is the confirmatory biopsy done with more cores or using a different technique to better sample the prostate?

Dr. Klotz : Yeah, that's a good question and partly because this area is changing from from month to month because of the advent of MRI, but the way we have done it for 15 years is its done with transrectal ultrasound guidance. Its the same number. Its somewhere between 10 and 14 cores. Its just the area that's targeted are the areas that tend to get missed and there are really three areas – the front part or the anterior prostate, another area out to the side called the anterolateral horn, and then the apex of the prostate. So, when we do it, we target those biopsies and the one thing I would say is that the people doing these biopsies should be guys who are used to patients being on surveillance because if its done by a radiologist who is not really thinking about it, he may not recognize that this is a surveillance patient who needs biopsy targeting these other areas. So, you need a practitioner who is on site, who is thinking about what he is doing.

So, our experience to date which overall, you know, has been positive with very few deaths, altogether at 15 years, about 3% of patients have died of prostate cancer. Most of those guys in retrospect look like that they

had microscopic spread of the disease before diagnosis. But, a third of the patients have been treated overall, most of them because they were upgraded based on the confirmatory results on the biopsy.

So, you know, our view and the view of many of my colleagues is that this approach works with implementation, but going forward, I think with increasing use of MRI, with MRI you find a target. So, I think, you know, if a patient is diagnosed with low-grade prostate cancer has an MRI and shows a target, we are going to start trying to put a needle in that target rather than just doing the more or less random or systematic biopsy and that's going to change how we look at this a lot. We are going to find more cancer because we are going to be putting the needle through the bull's eyes, that is just hitting it by chance and I think the challenge is going to be to avoid going back to where we were before, which is finding more cancer because its now a targeted biopsy and offering treatment again. If you follow me, we are going to have to sort of re-jig how we think about these patients because we find so much more cancer when we start putting the needle in a lesion that we see on imaging study as compared to just doing it systematically. I hope I have answered your question.

Thank you, doctor.

Thank you.

Priya : The person, caller using (5852)442-192, please ask your question.

Caller : Hello, Dr. Klotz. This is Herman and could you talk about Gleason's 7 patients, especially the 3+4 because that's right on the borderline and I think its all the more difficult and also you didn't mention anything about the genomic analysis that's now available like Oncotype DX and something else called something like Polaris, I am not sure if I got that right, that is useful in determining whether treatment is needed or not or what kind of treatment is needed.

Dr. Klotz : Great question! So, first of all, take the Gleason's 3+4. So, the basic message is Gleason's 3, as I mentioned, doesn't seem to have the hallmarks of a true malignancy and Gleason's 4 does. Gleason's 4 is a real cancer. If the patients came through Gleason's 4, there are 8 which tend to be a lethal disease, often incurable. So, these two patterns are like night and day and as soon as you have any significant amount of Gleason's 4, I think that that patient has a real disease and should be treated. The problem is that you have alluded to. Sometimes you get these patients with a very small amount of cancer on the biopsy and it may only be 5% of Gleason's 4. So, you are talking about not even a pinhead, you are talking about a fraction of a pinhead, of a couple of microscopic fields showing what looks like higher-grade cancer.

Another wrinkle in this area is pathology is an art as much as its a science. So, there is what's called between-observer variability. One man may call it 3+ 5% 4, one pathologist, the other may call 3+3. So, at the margin where you have a small amount of cancer with only a small percentage of that being Gleason's 4, we think those patients in many cases do as well as the 3+3s and we have evidence for that based on our series and there's another one from San Francisco, another one from Holland. They all show the same thing, that if you select some of these 3 + a little bit of 4 patients, they do just as well as a 3+3. Its a tricky area because no question, higher-grade prostate cancer can be lethal, you don't want to under treat these guys, but I think particularly in older patients, we have offered surveillance to men over 70 who have 3+ a minority of 4 and they have done just as well as the ones with 3+3. So, you have got to scrutinize them closely. All these patients now get an MRI in my practice. If they have a big mass or tumor on the MRI, that's a different story. They are not surveillance candidate, but I think the situation going forward is going to be guys who have 3+ a little 4 and a negative MRI, my guess is they are going to do very, very well with surveillance and they probably don't need treatment. As far as the biomarkers, so there are two FDA-approved biomarkers now, Oncotype DX and Polaris. They both are based on tissue. So, they do genetic profiling of the cancer and the biopsy and they give a risk score and that, I think, has tremendous potential to say, you know, this guy, he's only got 3+3, but his risk score is high. Another way to identify the bad actor early on. The challenge is that the biomarkers are competing with the emergence of MRI and in other areas in oncology where you have… Hello?

Yeah, still here.

Yeah, okay.

Another area is oncology. We have really good imaging. That tends to replace molecular profiling to some degree and you can imagine a patient who has got a little bit of Gleason 6 prostate cancer. His MRI shows a great, big, high-grade cancer in the front part of the prostate and you have as an alternative, the biomarker and you are asking that little tiny few cells of Gleason 6 prostate cancer to tell you that there is a great, big, high-grade cancer in a different part of the prostate. Its a real challenge for a biomarker to do that. I think in the long run, these will be complementary and probably there are going to be patients who may benefit from both cause coming through it as well. You know, the cost adds up. At the moment, if I have the choice between having an MRI and having the biomarker, I would put my money on the MRI and maybe have the biomarker as the backup, but this whole area is losing very rapidly and is probably going to look quite different in another two or three years.

Caller : Okay. I have had both, but anyway thank you very much, Dr. Klotz.

Dr. Klotz : All right. I hope they helped you.

Priya : We have received lot of questions via e-mail. I am looking through them and I think we have covered almost all of them through the course of our discussion and there's, however, one on spontaneous regression, doctor, which says should there be a more clear focus on spontaneous regression and should men with a diagnosis suitable for active surveillance be told about spontaneous regression?

Dr. Klotz : Yeah. So, spontaneous regression, just to clarify, means actually the cancer disappears and there is certainly some tumor sites where because the tumor lacks the ability to grow or lacks the ability to create new blood vessels or it has the cells age and they die unlike most cancer cells which are considered immortal, you can have this phenomenon. Its thought to be fairly common in breast cancer, for example. I must say my view of this is that in a majority of patients who don't progress its because the disease in indolent or its very slow growing, very stable. Its not going to disappear. We actually don't know for sure whether this happens or not very often. My guess is probably it does happen once in a while, but in the majority of patients, the cancer doesn't go away or disappear. It just sits there quietly. From the perspective of the patient, I am not sure it makes that much of a difference. In other words, does it matter whether they have a few cells that sit there quietly for the rest of their life or whether those cells disappear amounts to the same thing. They don't have a life-threatening problem and they can be managed conservatively. Its quite an interesting biological question right now in the field of oncology, we don't really have an answer in prostate cancer.

Priya : Thank you, doctor. We have actually completed our airtime. Dr. Klotz, thank you so very much for being with us today. Mike, Tony, Walter, and Tom, thank you for your participation. I greatly appreciate it. I thank our audience and hope you will all join us again for our next show on prostate cancer. We are having Dr. Ian Thompson of University of Texas Health Sciences Center as the expert on the show and its going to be in June 2014. Please visit curepanel.carefeed.in for information on our upcoming shows. The link for today's discussion will be sent via email to all participants. Cure Panel is back on 28th of March with an episode on multiple myeloma where we will be discussing clinical trials and treatment options at MD Anderson with Dr. Robert Orlowsky. Thank you, everyone. Thank you for the great discussion.