Prostate Cancer Controversies: PSA Screening; Treatment or Observation for Early Disease

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By Ian Thompson, MD [1]

We discuss the current controversies in prostate cancer—PSA screening and approaches to initial treatment for men diagnosed with the disease.

We speak with Dr. Ian Thompson, professor and chairman of the department of urology at the University of Texas Health Science Center in San Antonio, where he leads clinical trials for prostate cancer. We are discussing controversies in both screening men for prostate cancer, and approaches to initial treatment for men diagnosed with the disease. The US Preventive Services Task Force issued finalized guidelines earlier this year stating that the small potential benefit of PSA screening in asymptomatic patients does not outweigh the expected harms for slow-growing and not life-threatening cancerous tumors. And, a large study published in the New England Journal of Medicine, showed that men with early-stage prostate cancer treated with radical prostatectomy did no better than those actively monitored without surgery.

—Interviewed by Anna Azvolinsky, PhD

CancerNetwork: Dr. Thompson, you are one of the authors of the American Society of Clinical Oncology (ASCO) provisional clinical opinion on screening for prostate cancer using prostate-specific antigen (PSA) testing. The opinion was published last month in the Journal of Clinical Oncology. What were the major recommendations offered and what are these based on?

Dr. Thompson: So the recommendations were based on an evidence-based report and the recommendations that were made were basically three. That is, a man who has a limited life expectancy, say less than 10 years, probably does not benefit from PSA testing. The second recommendation is that the man who benefits is the opposite of that—has a life expectancy of 10 or more year. And the final one is one that I think every organization would agree upon: all men who are considering PSA testing should be informed of the pros and cons and should make that individualized decision in consultation with their physician. So that obviously differs from the task force. The task force actually has a very thoughtful document in its entirety but the task force's format is in such a fashion such that it gets distilled down to a letter grade and a single statement and they recommend against PSA testing. Within the task force recommendation they do say that a man may opt to discuss with his physician the concept of PSA testing. It's just that up front, the task force said "don't do it." The ASCO provisional guidelines stated up front, have a conversation with a physician and on an individual basis make an individual decision.

CancerNetwork: I see. In creating both of these guidelines, the committees used similar data sets? My question is why come to different conclusions?

Dr. Thompson: Well, actually, a lot of it depends on how you look at the data and how you value the data. The real quandary in all of this is that we would like to think that a randomized trial will answer every single question and there are two randomized trials with regard to PSA testing. The US trial found no difference in prostate cancer death rate and the European trial found a significant reduction although, many, many men had to be tested, and many treated to reduce the risk of death for one person. So, it is a value judgment, but additionally I think a lot of us look at the two trials and ask ourselves the question: Do they answer the question definitively? And the problem with the PLCO trial, which is the US trial, is that it was conducted as the PSA-testing almost-epidemic began, such that the arm that was anticipated to have minimal PSA testing had at least 50% testing if not more. So, it was really more intense PSA testing, slightly less PSA testing, and when you look at the report of the study, you see there was a whole lot of prostate cancer detected in the no-screening arm. So it is not surprising that there was little difference in prostate cancer mortality. The European trial had less of a distinction so that is likely why there was a difference. But unequivocally there are risks and benefits and I think all of us in the field would say "A man who is elderly or has comorbidities stands to benefit very little, and a man who is considering PSA testing should understand the downstream consequences—the benefits and the risks." It is unlikely that every single man will come to the same
conclusion and that is OK. It is an individualized decision.

CancerNetwork: So what are the current trends for PSA screening? As a clinician, do you feel that most men want to be screened despite recommendations? And how do you feel that the trends will change over time?

Dr. Thompson: I think currently we are seeing somewhat of a steady state. I am aware that some physicians have taken the primary recommendations and stopped PSA testing. And so I have not seen that much of a difference but I am reassured that many physicians that are very well educated in the nuances of the literature have come to the same conclusion that ASCO has come to. But I also worry, concurrently, about some physicians, who have had previous plans to do PSA testing and who use the guidelines to say "well, I am not even going to offer it or even have a discussion with the patient about it." And I am sure that is going to happen and for the man who, say is African American, whose dad died of prostate cancer, who may be of a socioeconomic status as to not be aware of PSA testing. That man may not have sufficient information to ask his physician. And the guidelines are pretty clear. It says, "don't recommend it, don't do it," and it seems to me that the physician may come to the conclusion that even in a high-risk man, that he is not going to offer it. That's why I think that the ASCO guidelines are a much more well balanced set of guidelines for how to do this.

CancerNetwork: There has been a new noninvasive blood test for prostate cancer detection that was approved by the FDA in June. It is called the Prostate Health Index. The makers of the test claim it is more specific than the pure PSA test, as it measures three PSA-related components and that the test will be cost effective. Have you had direct experience with this test and what is your opinion about it?

Dr. Thompson: We have a lot of experience with that. A large validation trial was conducted through the Early Detection Research Network of the National Cancer Institute. One of the components of the test, which is the pro-PSA component of the test, is a serum-based test that significantly enhances detection. It improves both sensitivity and specificity. The scientific lingo is that it pushes the ROC curve. And the test also includes percent-free PSA. And so these additional markers will indeed help with improving detection of some men who would otherwise not be recommended to have a biopsy and potentially reducing the number of biopsies in the men who will prove not to have prostate cancer. I will tell you, and put a plug in and a disclaimer here, that we are the developers of a web-based test called the Prostate Cancer Prevention Trial Risk Calculator. And we actually include free PSA and pro-PSA and a urine-based PCA3, as well as a number of other biomarkers and markers. Bottom line is that today we don't do, I don't do, prostate cancer early detection with just PSA. I incorporate a wide range of measures and markers to help more precisely determine a man's risk.

CancerNetwork: Being at an academic center, I am sure other academics also use the same approach, but do you feel that this approach is being taken up by community oncologists?

Dr. Thompson: That is a really good question. I think that it could be far better. It is often times at national meetings of oncology, urology, family practice, prevention, and so forth, that you see these epiphanies that occur as physicians who have never used risk assessment tools begin to realize that a PSA of 2.5 in a 55-year-old man with no other risk factors means he has an ultra-low risk of aggressive prostate cancer and that same value in an older African-American man who has a history of prostate cancer, it may be a five- or ten-fold risk, so there needs to be more education, no question.

CancerNetwork: As a final question, another major issue is whether initial surgical intervention is better than observation in men who have early-stage prostate cancer. The PIVOT trial, recently published in the New England Journal of Medicine showed that after 12 years of follow-up, those men who had a radical prostatectomy didn't fare any better, in terms of length of life or death from prostate cancer, compared to the men who were monitored but not operated on. What is your interpretation of the results?

Dr. Thompson: Well, Cathy Tangen who is one of the world's most foremost biostatisticians, she helped me write an editorial for the New England Journal of Medicine on this. The PIVOT trial was remarkable because Dr. Wilt and his colleagues managed to randomize 731 men with localized prostate cancer treated with surgery vs nothing. That was an enormous undertaking, and they should be applauded for it. Unfortunately, the trial was designed to have 2,000 men in it, and Kathy and I looked at it and our concern is that there may not be enough events, the prostate cancer recurrences and deaths to be able to tell with certainty what the impact may be. And in fact, if you look at the confidence intervals, there could be as much as a 50% reduction in death from prostate cancer treatment. But nonetheless, the thing that really points out is two things. Number one, most men who are treated for prostate cancer with surgery or radiation don't need it. Many, many men, especially those with...
low-risk prostate cancer do very well with simple observation. And so men with low-grade, low-volume disease, older men, with intermediate-risk disease should seriously consider surveillance to avoid side effects of treatment. On the flip side, it also showed in a subset analysis, and I would totally agree with this, that the higher risk men, are the ones who are most likely to benefit from treatment. That is probably the take home message to the average practitioner—that low-grade disease, you can treat it, but you are going to be treating a whole lot of people to help only a handful. But high-risk disease—don't forget about the fact that this tumor takes the lives of 30,000 men or so per year and those are the tumors that will take a man's life and who we know from randomized trials we can make a difference in reducing mortality.

CancerNetwork: Are there any currently ongoing trials or one that will soon start that will further address this tension between treatment and monitoring?

Dr. Thompson: Absolutely. Dan Lin and Pete Nelson from the University of Washington and the Fred Hutchinson Cancer Research Center are leading a study called the Prostate Active Surveillance Study. There are over 700 men that are currently enrolled, ultimately to have 1,000 men in this study. And it is men who have opted for active surveillance. And in these men, it is a biomarker-driven trial. We are collecting urine and blood and other information such as biologics, including snap-frozen biopsies in these men, and the goal of this—if you imagine out of 1,000 men, maybe 100 need to be treated, maybe 15, certainly not 500. So as these men are monitored, we will be able to monitor those who ultimately need to be treated and we will know by looking back at the bio-repositories what are the signatures of the men who need to be treated. So that ultimately, the view of the future looks something like this: man comes in with newly diagnosed, well first, the man will come in with a variety of markers to determine whether he is at risk for high-grade disease. If he is at risk for high-grade disease, a biopsy is done. And then, the tumor gets categorized. Is it a tumor that needs to be treated or not, so that ultimately, the only guys who are given biopsies are those men who have life-threatening disease. And the only guys who get treated, are the men who will benefit from treatment. So we can reduce the burden of treatment and diagnosis and improve the outcomes. So I am very, very optimistic that we will have a future in which we do much more precision diagnosis and precision treatment.

CancerNetwork: Thank you so much for joining us Dr. Thompson and sharing your knowledge.

Dr. Thompson: My pleasure, thanks for the invitation.

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