Diagnosing Aggressive Forms of Prostate Cancer With New Imaging Tests and Biomarkers

On this show we have the Associate Director, Department of Urology, Roswell Park Cancer Institute Dr. James Mohler discussing the recent NCCN guidelines for prostate cancer treatment and the latest research available to us that can help diagnose high risk forms of prostate cancer and avoid unnecessary treatments for low risk forms. Tune in to get a better understanding of prostate cancer treatments and its management.

Full Transcript:

Priya Menon – Good evening, everyone, and welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at CureTalk, joining you from India; and I welcome all of you for a discussion on prostate cancer. All Cure Talk shows on prostate cancer are conducted in association with the Prostate Cancer International and the Prostate Cancer Foundation. This is the seventh time we are discussing prostate cancer on the Cure Talk platform. On our previous episode on prostate cancer, we discussed clinical trials with Dr. Ian Thompson from the University of Texas Health Science Center. On this show, we have the Chair of the Department of Neurology, Associate Director, and Senior Vice-President for translational research at Roswell Park Cancer Institute, Dr. James Mohler, discussing national guidelines for prostate cancer treatment. [start=01:15,01:41Priya_Menon] Dr. Mohler who chairs the National Comprehensive Cancer Network's prostate cancer treatment guidelines panel will also highlight the latest research available to us that can help diagnose high-risk forms of prostate cancer and avoid unnecessary treatment for low-risk forms. Welcome to Cure Talk, Dr. Mohler.

Dr. James Mohler – Thank you very much.

Priya Menon – My co-host for the show is Michael E Scott. Mike is Co-founder and President of Prostate Cancer International, Health Strategist of Calcium, Member of the Board of Directors of the National Organization for Rare Diseases and the International Myeloma Foundation Supporting Dr. Mohler and Mike on the panel are experienced and knowledgeable prostate cancer survivors and advocates, Tony Crispino and Paul Carpenter. Tony Crispino is a patient advocate at SWOG, where today he works with some of the industry's finest researchers on the latest clinical trials. An advance disease survivor himself for over six years, Tony has run online discussion forums, live support groups, and is currently the President of UsTOO Las Vegas and a member at the American Society of Clinical Oncology. Paul Carpenter is a patient advocate for men diagnosed with prostate cancer. He has contributed to dozens of online groups and forums and also co-founded a Los Angeles support group for gay and bisexual men living with prostate cancer. I extend a hearty welcome to all panelists and to all our listeners. Towards the end of the hour, we will be discussing questions sent in via email. You can mail your questions to priya@trialx.com; or if you want to ask a question live, please press 1 on your keypad and we will bring you on air to ask that. With that, I hand over to Mike to begin the discussion. Mike, you are on air.

Michael E Scott – Good afternoon, Dr. Mohler. Thank you very much for taking the time to join us.

Dr. James Mohler – My pleasure.

Michael E Scott – One of… We had asked you, I think in the prior part of the program, to talk to us a little bit about some of the evolving issues in the diagnosis of prostate cancer particularly. In the most recent update to the NCCN Guidelines, we have obviously noted that you have included information now about the potentially appropriate use of multiple-parametric MRI in diagnosis and also in active surveillance, and you have mentioned also the issue of the multiple new genetic engineering tests that have come into market that

clearly is felt for the patient community additional guidance about when people feel these are more or less appropriate forms of testing would be extremely useful. So, I would be interested in you talking a bit about some of the most recent and important updates to the NCCN Guidelines but also focusing on those two particular issues, if you would care to do that for a little while.

Dr. James Mohler – – Yeah. I would be happy to begin our discussion that way. Its been very interesting for me to watch my colleague, Peter Carroll, over the last two years improve the prostate cancer early detection guidelines. I think they have been made much simpler and therefore much more user friendly; and I urge all your listeners to pay careful attention to the simplification, which is largely encompassed in the second page of the guideline Pros B2. We are very particular about the use of PSA for early detection and for guiding treatment because we discovered it here at Roswell Park. I still think that PSA is best used not as a snapshot, in other words not just paying attention to what a value is on a given day, but its most valuable when its used in conjunction with prior values so that you are able to look at what we call PSA kinetics, whether you do that by calculating a PSA velocity or a PSA doubling time. This additional information provided by PSA then makes many of the nomograms much more useful and can personalize the use of PSA to your particular situation, especially when you combine what your PSA kinetics are with your own age and health and other parameters such as your digital rectal exam, your family history, etc., etc. So, now that brings us to how to use a PSA to prevent a man from suffering from PSA anxiety and I frequently say that should perhaps be a new psychiatric definition because so many men are so focused upon their PSA, both men who don't have prostate cancer and as well and more appropriately so those men who have prostate cancer where PSA is far more valuable for monitoring their disease, but I think what the Sloan-Kettering group has shown us is that if you are fortunate enough to have a low PSA, you don't have to get anxious every year or in some cases some urologists even use a PSA every six months, which is absolutely no data that they should be performed that frequently, but if your PSA is less than 1 and you are less than 50 years old, you are in a very, very good place and you probably don't need another PSA until you turn 50 years old. Now, if you are higher risk group such as you are African-American, you have a first-degree relative with prostate cancer, you probably want to get a PSA a little more often, maybe every year or two. The modeling suggests that every two years is optimal and then when you get to that 50th birthday, the current NCCN Guidelines recommend PSA every one to two years and again you can tailor it based upon your risk factors. And as long as your PSA stays less than 3, you are in a pretty good group and then you should begin to think as you get older about whether its worth the risk of having a prostate cancer detected that you didn't want to have detected, in other words that you are not going to live long enough to suffer a death from prostate cancer and hence why know about it and more importantly, why suffer the consequences of side effects of treatment when you probably didn't need the treatment in the first place. So, we are encouraging men when they reach a physiologic age of 70, notice I didn't say chronologic age, but if physiologic age of 70, they probably can forego any additional PSAs. If we did everything I just mentioned, if we complied with the NCCN Guidelines, we would see a tremendous reduction in the cost, both financial and anxiety wise, associated with overuse of PSA which leads to over detection of prostate cancer.

Dr. James Mohler – So with that as the baseline, let me now talk about the use of multi-parametric MRI, and this is a three-part study which then requires a rather sophisticated computer analysis of the images to calculate some new medical data that allows radiologists to assign low, intermediate, or high risk of a lesion being an aggressive prostate cancer. We are learning a lot about three-parameter MRI or multi-parametric MRI, and it appears to have an advantage that it rarely sees the little well-differentiated cancers that I call autopsy-type cancer that all men get as they age. Your chance of having that type of cancer is about the same as your age in percent. So, I am 61 years old, I have a 61% chance of talking to you today, having a indolent prostate cancer in my prostate. Now, I don't want to be biopsied to find that out and it appears an advantage of the multi-parameter MRI is it doesn't see this type of cancer and it may see the aggressive ones. So, right now, when a man has an elevated PSA and has a negative routine biopsy, the NCCN Guidelines suggest that a multi-parameter MRI may be appropriate to make sure you are not missing on aggressive prostate cancer. In addition, MRI might be useful in treatment planning for men who are concerned whether neuropreservation is appropriate or not when they have a bulky prostate cancer or a prostate cancer that is poorly differentiated. Then, the last way to personalize your prostate cancer

situation is to take advantage of the new molecular tests that are available and there are many of them and that's confusing many men and many of us urologists as well. There are three about which the most is known at the present time. These are the assays from Prolaris Corporation, the Oncotype DX prostate cancer assay, and the Decipher assay and each of these takes advantage of the expression of genes that are by the prostate cancer that can be used in most cases to guess at the growth rate and hence the aggressiveness of the prostate cancer. So, some of the tests recognize an aggressive cancer, others recognize the absence of an aggressive cancer and so some men who should be undergoing active surveillance of a low-risk cancer might find themselves more able to live with the anxiety of watching something called cancer if they knew that a molecular test is consistent with a low growth rate. Other men faced with an elevated PSA might like to take advantage of newer ways of analyzing PSA or a different test than can be performed on the urine or the serum that might help them to decide whether they should have a biopsy or not and if they are fearful of missing an aggressive cancer. So, these new molecular tests are coming along at a very rapid rate. They go through a very different approval process with the FDA and so if I wrote in the NCCN treatment guideline, I am a little concerned that we are going to have to depend on the market place to properly position now, as to whether they are valuable to help men with their decision making or not and in the meantime, we don't have clear evidence that they will help with decision making. That will need to be accumulated and so many of the insurance companies are declining to pay for these and the common denominator to many of these tests is they are quite expensive.

Michael E Scott – If perhaps I could just ask a couple of questions, Dr. Mohler, for clarification. My understanding is that the MP-MRI test is available at a relatively limited number of centers at the present time. It does require some very sophisticated pathological skills in order to interpret the imagery and this sort of thing. So, I am curious as to how fast you think that that technology is starting to spread out into the border community, and the other question I was going to ask you, what was very specifically about the PCA3 test where we are seeing some fairly…, some differences of opinion about the value of the test.

Dr. James Mohler – All right. So… I always have trouble remembering more than one question at a time, but I will try and handle this. So, let's take the multi-parameter MRI first. This is a technologically demanding test that requires basically three MRIs in one. It has to be done on a 3T magnet and then it requires a rather sophisticated analysis of the images. So, that's sophisticated software, but most importantly you have to have an experienced uro-radiologist who is very good at interpreting these. So that its not enough for a man to go and say, you have a 3T magnet or are you capable of analyzing all three parameters of a complex MRI, but you also have to know do they have a radiologist or radiologists highly skilled in this area. So, we are very concerned that the results that are being published now largely as single-institution experiences are going to be very difficult to disseminate through community practices and even smaller academic settings that don't see as many patients with prostate cancer. So, this is another example of where its not just the technology, its the people that go with the technology that are going to make this valuable and if this can't be disseminated its going to have to stay in centers of excellence and then patients are going to be inconvenienced because to realize the value of a three-parameter MRI in these particular situations I mentioned, they are going to have to travel. The other thing I should mention about three-parameter MRI is if you have one shortly after a prostate biopsy, it will be uninterpretable because of the bleeding and inflammation that results from the biopsy. So, I am already seeing far too many patients that have a diagnosis of prostate cancer and then the next week have a three-parameter MRI and are told that their cancer is really advanced or they can't have their nerves spared or whatever and all the radiologist is doing is confusing the bleeding and inflammation that results from prostate biopsy with an aggressive cancer. With regard to the PCA3, this test was developed by a good friend of mine. So, I don't allow that to bias me. All of these tests that are used to help a man decide what to do when the PSA is between 2.5 and 10, I do not believe they have been critically enough evaluated in the context of PSA kinetics. Its very important that these tests give added information above and beyond PSA kinetics, but what I just said is very controversial. Its kind of my personal opinion and I hate to do this to patients out there, but this is an area where more research is necessary. It is very important. I still believe personally that I would rather see PSA values measured once a year for several years than any test of PSA derivatives or alternatives to the PSA test at this time based on what I know, but this is not my particular area of expertise, so I wouldn't take what I said to the bank.

Michael E Scott – So, I am sure we are going to have lots more questions for you that we can come back to, but I think at this stage what I would like to do is ask my other two panelists if they have questions and perhaps we could begin with Paul Carpenter because I am sure Tony has got six written down and Paul might only have three or four.

Paul Carpenter – Well, thank you for that, Mike. This is Paul Carpenter. Dr. Mohler, you mentioned the three well-known genetic tests from Prolaris, Octotype DX, and Decipher. All of these, at least as far as I know, seem to take the scattershot approach of looking at a few dozen high-profile genes. Are there other forms of genetic testing perhaps still in the works that take a different approach other than the scattershot?

Dr. James Mohler – Well, I am not sure exactly what you mean by scattershot, but… Umm….

Paul Carpenter – Well, I can clarify and it looks at say, as I recall, Prolaris looks at 46 different genes and has a rather complicated waiting algorithm. These genes are protective. These genes are susceptible and comes up with a single number looking at their algorithm.

Dr. James Mohler – Yeah. Prolaris actually uses 31 genes that were selected A priority. These are genes that are associated with cellular proliferation and so that's why I say its not exactly a scattershot. Now, the Oncotype DX test looked at more of a scattershot of genes and then arrived at a group of 17 that seemed to convey the prognostic information. Decipher is even more of the scattershot and that it seeks to look at all genes that are expressed plus genes that are not expressed and it allows the outcome to derive the predictor. So, everyone of these has a little bit different strategy and has different aspects of how much of a scattershot it is versus how much a human thought went into to, I won't say biasing the assay, but directing the assay. So the most interesting thing to me is that these three major companies that we have talked about, I am very impressed with the way they are going about the development of these tests, how open they are, how participatory they are with the academic research community, and I believe they are even having some discussions about cooperating to see which of the tests provide the best information in which situation. So, I really look forward to a future where we know which test to use when and most importantly whether we can make these tests better as they are used more and more.

Paul Carpenter – That sounds very hopeful. One thing that I wanted to respond to was less hopeful when you said, if I understood correctly, the NCCN, it does not yet have, I don't know, the budget or the expertise to evaluate this rapidly evolving field and for the time being we are going to have to depend on market forces. I worry about that. I wonder if you could comment any further.

Dr. James Mohler – Well, the biomarker development is a completely different field of medicine. Its under a whole different system of regulation by the FDA then as drug development.

Paul Carpenter – Right.

Dr. James Mohler – The NCCN does not conduct clinical trials. NCCN is an organization that relies upon assembling panels of experts to review newly published information and where sufficient information does not exist to provide expert opinion as to the best way to go. The section on molecular testing in the NCCN Guidelines, which is manuscript page 4, every word was very carefully chosen to not over promise, to not be too excited to be realistic, and to call for additional testing where necessary. So, right now, its a tough decision whether to use any one of these tests because they have not been rigorously tested as to whether they result in decision making that is better or not. Most of the studies have been done using what's called retrospective-prospective analysis where you are looking at bank specimens where the outcome is known. Problem with prostate cancer, as you all know, is it grows so slowly even when its aggressive that if we are going to use these tests to guide our future decision making and then look at an outcome like survival, it, you know, my grandchildren are going to have to interpret those studies.

Paul Carpenter – Yes. I quite appreciate the dilemma or the trilemma facing you in trying to keep up with the evolving technology and I was just curious to know how do you guys keep up and thank you for your

answer. [rend]

Tony Crispino – This is Tony. How are you all doing and happy new year, Dr. Mohler. I would like to kind of elaborate little bit on where you just went with retrospective views of trying to get some significant useful data. Clearly, randomized clinical trials is going to be a problem, especially anything that involves an active surveillance patient because they have to be for long and very expensive. Currently, at SWOG we are looking backwards, like you said, into the bank, and we are lucky to have the PCPT in the select banks that exist for us, but going backwards and looking and compiling some data and trying to arrive at some reasonable hypothesis for a clinical trial. Can you mention any other types of backward-looking banks that might be useful in helping us get some data until such an RCT can eventually be done?

Dr. James Mohler – Yeah. So, there are many banks that archival specimens at all our academic centers. The problem is that a tissue biospecimen only has value if you have outcome connected to it and so again, I don't like to say what's difficult to do, but its easy to collect a bunch of archival prostate tissue from men with cancer. Its harder to annotate those specimens with good clinical data so you understand exactly who it is you are looking at and then its even more difficult to follow them or to have followed them for a period of time necessary for them to declare whether whatever you are seeing in the tissue predicted that outcome or not. So, I will give you a simple example. One of the biggest problems in prostate cancer right now is the man who undergoes potentially curative therapy and the only evidence of disease recurrence is a persistent or a relapse by PSA. Yet a man who has a PSA detectable after failed curative therapy has a mean prostate cancer limited life expectancy of about 20 years. So, surprise, surprise! We can't get anyone interested in conducting clinical trials in this phase. Now, you asked about active surveillance and let's go backwards if that's even worse. An active surveillance patient with an autopsy-type prostate cancer that I talked about or they are NCCN low risk or very low risk, they have about a 20% to 30% chance of progressing to some form of treatment. If that treatment in an active surveillance population is going to be nearly a 100% curative and so you are never going to know whether they actually needed to be treated or not because all of them will be treated and the curates will be virtually 100%. Now, you are going to compare that to people on active surveillance who show no evidence of progression and because you detected their cancer by PSA, it will be at least 10 years before they would have developed a nodule and we know from them that the mean life expectancy is on the order of 12 to 15 years. So, you can see the simple numbers game and the expense associated with any type of trials in this work space whether you are beginning with already acquired tissue or you are trying to do something prospectively just because of how slow growing prostate cancer is.

Michael E Scott – So, doctor, now that raises an interesting question about whether and I am not going to try and hold you to anything in particular, but has the NCCN committee actually discussed the issue of the possibility of changing the nomenclature of low-risk prostate cancer?

Dr. James Mohler – We have had discussions about that. In fact, there was a very excellent debate between Jonathan Epstein from Johns Hopkins and from Cornell… Mark….

Michael E Scott – Rubinstein.

Dr. James Mohler – Mark Rubin. Thank you. I am so bad on names. Mark Rubin from Cornell, where they debated whether NCCN or AUA low-risk prostate cancer should be renamed, whether Gleason grade 3+3=6 prostate cancer in essence should still be called prostate cancer. And it was a very interesting debate. It produced lot of questions from the audience and they actually had each of them argue the other one's physician, so it was all so rather amusing. Now, we all know that there are Gleason grade 3+3=6 prostate cancers that are mis-graded either because of sampling errors or they possibly could turn into more aggressive cancer with time. So, I don't think its a good idea and the NCCN panel did not want to get into a renaming. I think what people need to understand is that NCCN very low risk and low risk prostate cancer are extremely unlikely to ever cause your death and should only be treated if there is evidence of growth, but our problem is we are still arguing about what should be the proper criteria for evidence of growth and that brings us all the way back in a 360-degree circle to the molecular markers as to whether they can better

detect a prostate cancer that's growing rather than what I actually rely on quite heavily, which is PSA kinetics from the time of diagnosis, but there is a very excellent paper from Hopkins cautioning that PSA kinetics will not detect everyone whose cancer is progressing, but again as I said before, if you find evidence of progression by biopsy and treat everyone, you will never know whether you really had to treat them all. I just want to convey to the audience that how difficult this whole area of investigation is. So, I understand why its frustrating to patients, its frustrating to us, but its also what makes it so interesting and all the uncertainty connected with virtually every aspect of prostate cancer should empower patients because you can evaluate the inflammation and make whatever decision you wish because no matter what decision you make, somebody will tell you its right and somebody will tell you its wrong, so you can make the one that's best for you and then just don't pay any attention to everybody else.

Michael E Scott – I don't know if you actually saw this, but there was a very interesting paper from Australia just the other day on decision analysis looking at the ways Australian men make decisions, about whether they should or shouldn't have PSA tests based on the risk of the potential futures that they will be faced with if they were diagnosed or not diagnosed or had to pay for certain types of therapy or whatever. I mean, it didn't resolve the problem in any way, but it did give some very interesting perspective to help people, help patients' thought based on their age and whether they have had PSA test before or things like that.

Dr. James Mohler – No, I have not seen that paper, but we need to do a lot more research about decision making.

Michael E Scott – Right. I have your email address. I will see if I can find that. I will see if I can send it to you because the hospital was kind enough to send it to me.

Dr. James Mohler – That would be great.

Michael E Scott – Paul, to get back to you, do you have another question?

Paul Carpenter – Actually, this sort of ties in with what we were just arriving at and that is the balance between the quality of life and length of life and that's a balance that every man facing prostate cancer has to come up with, implicitly or explicitly, I think the NCCN Guidelines make some kind of determination that if PSA testing is done this early an age, there might be so much over treatment; if its delayed until later and so forth, and I am wondering who do those factors be made explicit, have they been made explicit as to, for example, in Great Britain there is a quality-of-life year, the quality…, I forget what I stands for. I am wondering if NCCN has anything similar to make explicit its guidelines for whatsoever under treatment for too many people.

Dr. James Mohler – Right. So, the term that you are trying to find is quality-adjusted life years remaining.

Paul Carpenter – That's it. Yes.

Dr. James Mohler – Right. And that… And that the problem with that is it is subject to the values of an individual.

Paul Carpenter – That's what is going to be my followup question.

Dr. James Mohler – Yeah. So, one man… One man you will say to him, if you undergo radiation, you will have a 70% chance of being impotent 10 years from now and he will go, well, that's no big deal, I will be 70. The next man will go 70%, I am not doing that. So, the quality adjustment has to be done for each individual person and is very complicated to do correctly, and so typically that type of research is done on a population basis where when we are sitting in, doctor-patient, in an examining room, you have to do it for an individual and that's where this is so difficult because statistics apply to the other 99 guys. They don't apply to me and so what you have to do is present the statistics and then allow the patient to decide where

they themselves fit amongst all those statistics.

Paul Carpenter – I couldn't agree more.

Dr. James Mohler – Yeah. I am a big believer. My job is to educate patients. Its their job to decide what to do. At the end of a visit, I will say to them, you know, do you want me to, you know, like, when I was younger, I would say if you were my dad, this is what I would recommend. Now, its like, if you are me…based on what I know, I think I would do this, but statistics… You want to use statistics to inform people, not confuse them and you want to remember that all it does is give you that you are painting a broad picture with statistics, but then you have to figure out where you are going to be.

Paul Carpenter – I quite agree.

Michael E Scott – Dr. Mohler, people like Paul and Tony and I are often on the receiving end of questions from patients about the side effects related to treatment and one of the things that I felt over the years is that we are all faced with a problem that the side effects that's clearly erectile dysfunction and incontinence. Those are presented in papers related to the treatment of prostate cancer based on very different standards from institution to institution and often underplay the significance of those side effects to the patients in the sense that if you are going to get an erection at all, you are potent, which certainly is the way most men actually think about being potent. Would you care to comment on that?

Dr. James Mohler – You raised a very, very important point and that is that most urologists and radiation oncologists because of what they do, believe in what they do. In other words, if I got a nail, find me a hammer. What you have to do as the patient is you have to inquire carefully about the individual experience of the treating physician using their modality and if your physician is quoting, I always like to say Dr. Walsh's experience at John Hopkins, then you need to go further and there are some basic rules of thumb that Dr. Walsh actually advanced years ago, that a radiation oncologist or a urologist should have done in their career at least a 100 of what they are proposing to do to you and they should do at least one a month of what they are proposing to do to you. Now, I personally wouldn't let anyone operate on me that does a prostatectomy once a month and has done only a 100 in their career, but you got to look at this very carefully because the person that is the best radiation oncologist or the best urologist is the person who does the procedure relatively rarely but has really good results because they figured out how to do it safely and that's who I think we should be studying. There are lots of people out there that do thousands of procedures wrong and so you got to be careful here. Now, the other side of the coin. I just talked about numbers, experience. The other side of the coin is to specifically ask that individual, whether its a radiation oncologist or a urologist, what their impotence rates are, what their incontinence rates are, what their erectile irritability rates are. Most importantly, what's the secondary cancer treatment rate and if they can't tell you their own results, then you should go look for another person to treat you. All of us that are obsessive compulsive and good, have databases and we know exactly what our results are because if we stray from what we think is good, we got to figure out why and make an adjustment. Did I kind of answer your question?

Tony Crispino – Yes, part of it, yes, but the other part is it would really make people like me a lot happier if there were…, if everybody used the same standards for measuring things like erectile dysfunction and incontinence. Tony Crispino – I mean, we have got a lot better than we used to be, but there is still a lot of variation in the way its actually reported and published data.

Dr. James Mohler – Yeah. You are exactly right. When I came to Roswell Park 11 years ago, we put in place immediately because we were starting a robotic program, a standardized way of assessing the quality of life of everyone and we relied largely on Mark Litwin's instruments to do that, but there is not enough granularity in the UCLA instrument for erectile dysfunction, so instead we used the Sexual Health Inventory, the SHIM, but these instruments are out there. They are well validated and they should be being used by everyone to do exactly what you are recommending to use, standardized forms of evaluating the side effects of these different treatments. I want to come back to one thing that you mentioned earlier about active

surveillance. The NCCN Guidelines and I have been on a crusade about the need to right size treatment. So, what you don't want to do is treat everyone in who you can diagnose prostate cancer. By the same token, you wouldn't want to never treat anyone in who you can diagnose prostate cancer, but everybody lives in between those two extremes I just gave and what we are trying to do is right size treatment. So that those people who have aggressive prostate cancer get a lot of treatment and hopefully we can cure them and those men who have a low-risk prostate cancer can avoid treatment until such time that we can demonstrate that their cancer has really grown and we now know with this growing active surveillance experience, it now exceeds 4,000 men reported in the published literature that we have yet to have a single death once we recognize that we shouldn't have subjected the three patients in Toronto to active surveillance. We have not had a single death since in those 4,000 men. So, we now know that active surveillance is safe for many men and I am very proud that NCCN led the charge for this where we routinized our guidelines so that beginning in 2009 that men with low-risk prostate cancer and life expectancy less than 10 years, active surveillance was the only recommendation that should have been given and then we expanded that two years later to where if it was NCCN very low-risk prostate cancer and life expectancy was less than 20 years, active surveillance is the only recommendation that should have been given. This has two things of benefit to men. It avoids the side effects of unnecessary treatment, but it will also make PSA perform better. If we quit treating people that didn't need to be treated, then its one more step to quit diagnosing cancer that didn't need to be found and so I am very hopeful that we can right size PSA so that then it will be easier to right size treatment.

Michael E Scott – So, Tony, one more question from you and after that we are going to throw it open to people with questions from outside. So, one more from you, Tony.

Tony Crispino – Yeah. I have to back up a little bit here to the discussion of the multi-parametric MRI. Of course, the discussion here was in trying to detect higher risk cancers. Obviously, I think I would go back to Oliver Sartor who said that we are really good at finding the aggressive cancers and we are only pretty good at finding the less aggressive cancers. The MP-MRI, I am going to apply that standard and sit there and say, it seems to me like as though we should have good data today and where detected high-grade prostate cancer and we should have at least some good statistics there that show us that its got some success and then conversely, when the challenge is when we see that we don't see the characteristics in the imaging exams that tell us that its high grade, yet there is still a risk factor that it is.

Dr. James Mohler – So…, umm… The great advantage of the multi-parameter MRI is it allows you to carefully examine the anterior prostate. It is not immediately accessible to the examination finger nor is it sampled in the routine 12-core sextant biopsy. It is focused on the peripheral zone as we learned a long time ago, is the best way to detect prostate cancer. The anterior prostate by ultrasound is very heterogeneous, so its very difficult to see a lesion. So, the real advantage like, now when somebody has an elevated PSA and a negative biopsy, my routine has been when their PSA increases again, so then do a 12-core biopsy and then do two cores each of left and right anterior prostate, which we call the transition zone. Well, if you think about it, the transition zone is as big as the whole rest of the prostate, and instead of doing 12 cores, I have routinely done four and I haven't really directed into anything because I knew I couldn't see anything. Now, we were kind of assured because, in general, transitions zone tumors are less like to metastasize and often grow more slowly than peripheral zone tumors, but here we made a mistake because now that we can image the anterior prostate, we are recognizing that in these men who we haven't before detected their prostate cancer but have a rapidly rising PSA, we are finding an alarming frequency of high-grade prostate cancer in that anterior zone that before we simply didn't know about. So, I think its appropriate to use MRI in this situation, but you still need to perform the biopsy and I hope what you said is true, that we will then be able to cure these people because the literature has indicated that these anterior tumors are less likely to metastasize, but I am not sure that's going to prove to be true. Again, remember, three-parameter MRI is very new. So, we don't have the followup necessary to prove that its really of great value, although I believe its going to be proven to be.

Michael E Scott – So, Priya, can you hear me?

Priya Menon – Yes, Mike. I can hear you.

Michael E Scott – Perhaps we could now throw the questions open to the remaining audience if you can cater to that?

Priya Menon – Thank you, Mike. Listeners, if you have a question for our panel, please press 1 on your keypad and we can bring you on air to ask your question. Dr. Mohler, we have received lot of questions via email and I am just going through them. I see we have touched upon a couple of topics that the questions have come in through, but let us start with the most latest one, recent one that has been sent via email. Dominic who wants to know, what's promising for men resistant to ABI and Enzo? He is hearing mixed reviews on Galeterone and he asks, are anti-PD-1s the answer?

Dr. James Mohler – I can't answer and nor can anyone else about whether anti-PD-1s are the answer. I would say the short answer that is no. The anti-PD-1s are of great interest right now. They seem to work most effectively in men with advanced castration, I call it recurrent prostate cancer, who have BRCA1 or 2 mutations, but even when they work well, the cancers still find a way to get around the PD-1 and PDO1 inhibitors. So, no, they are not going to be the answer, but if you respond well and your response is of long duration, you will believe they are the answer.

Priya Menon – Thank you, doctor. The next question is, can you please discuss treatment for prostate cancer that has transformed into anablastic?

Dr. James Mohler – So, this is an area of great interest right now. The NCCN prostate cancer treatment guidelines have been completely redone for advanced prostate cancer with the 2015 edition. Many people believe, my medical oncologist friends, that they are seeing more of these neuro-endocrine and small cell cancers and their hypothesis is that better androgen deprivation therapy using the new agents is resulting in the evolution of these more aggressive, I will just lump them together as small cell-type prostate cancers. Again, this is largely anecdotal. Its unclear whether these cancers should be treated differently than garden variety castration recurrent prostate cancer, in other words should Taxotere still be the…, the dose of Taxo still be the primary chemotherapy in any regimen or should different agents be tried. Again, this is something that resulted in a change in the NCCN Guidelines and clinical trials of these small cell variantsce are going to give us more information in this regard soon.

Priya Menon – Our next listener wants to know, scientists and physicians are contemplating on combining using several biomarkers for accurate diagnosis of prostate cancer. He wants to know your opinion on that and whether this would increase cost of diagnosis as well as treatment that comes later?

Dr. James Mohler – So, I assume that your listener is talking about combining the different forms of PSA, which is called the 4… Again, I am so bad on names, the H4 score, I believe.

Michael E Scott – Yeah, 4k score.

Dr. James Mohler – 4k score, thank you, and there is also the methylation-based test. So, yes, they cost more than PSA and the question is, is it worth the cost? And again, if you can better right size diagnosis and treatment, they will in the long run prove cost effective. So, I am a big believer in trying to separate prostate cancer as best we can and to that which is aggressive and that which is unaggressive. If you are aggressive, then you need treatment and where I start to have a little bit of a problem with the use of the fancy assays is if I have already had my prostate out and I have a chance of recurring, what advantage is there to me to know whether that chance is higher or lower? Either way, I am going to worry and in that space you got to have a really good test because you go forward with an additional treatment, you have to be 100% correct that your potentially curative treatment has not worked. Again, I really like PSA for monitoring once the prostate has been removed or irradiated. Its very, very good in that situation. I am more excited about the use of the more sophisticated tests to select those men who should or should not be biopsied. I don't want to miss an aggressive cancer and there the question becomes what's the relative

value of the new molecular test versus a three-parameter MRI. In active surveillance population, I want to be able to reliably tell somebody that its safe to do active surveillance. So, I really think these tests will find their proper spaces early on in disease and I look forward to that happening.

Priya Menon – Our next listener wants to know, could you please elaborate on targeted biopsy and how it is better?

Dr. James Mohler – So, this is a burning question right now because if you have a three-parameter MRI that tells you where a high aggressive cancer might be hiding, you clearly want to stick a needle in it and you can do that by just putting a needle in the patient under MRI guidance. The only problem is that takes several hours and is very, very cumbersome to do. So, the idea is identify the lesion by MRI and then use your ultrasound to place the needle into where the lesion is. Now, there are two ways to do that. You can mentally fuse the images. You can work with your excellent MRI radiologists to figure out exactly where in the prostate that lesion is and then you can perhaps see it by ultrasound. I have had this happen several times now where I go, how could I have missed that, once somebody tells me that's where it is. That's called a mental fusion. The other possibility is that you can't see the lesion by ultrasound, but at least you can oversample that area of the prostate. Now, you can go one step further and you can fuse, There are now several vendors that have developed software packages that will take the MRI images and overlay them on to the ultrasound images and allow you to target the lesion seen on MRI while you have an ultrasound probe in your patient looking at the prostate. Again, it remains to be seen whether mental fusion is enough or whether you should have an actual software fusion of the MRI and ultrasound images.

Priya Menon – Thank you, doctor. The next… The next listener wants to know, what is the reason why PET scans have not been successfully used in prostate cancer diagnosis so far when this imaging technique has been successful in other forms of cancer.

Dr. James Mohler – So, a PET scan for the detection of prostate cancer has not been very useful. The only place you can get a choline PET/CT is Mayo Clinic where its being evaluated to see whether you can see using PET increased metabolism in cancers of the prostate. The basic problem with this, with PET in the prostate, is that the prostate is prone to inflammation and where we see inflammation, you will see increased metabolism and the way cancers are recognized is by increased metabolism. So, its going to be very hard to separate the inflammation that occurs in many men due to the stones within the prostate and other reasons from the cancers that might be within the prostate. Now, PET/CT is finding a way to perhaps give additional information beyond a standard bone scan when you do an F-18 PET and also in the research setting you can label DHT or testosterone and see where its taken up by tissues, for instance in the bone marrow that shouldn't ought to be there taking up, you know, androgens. So, I hate to say it again, but there's a lot of work in this area and PET scanning though at this time does not have a clear use for early detection of prostate cancer and is used for better staging of prostate cancer is in evolution.

Michael E Scott – So, if you are aware at this point, Priya, you know, I think our hour is nearly up and I did particularly want to thank Dr. Mohler for his time but also I wanted to thank him and all his colleagues who worked with him on the NCCN for the hard work they put into the constant updating of the NCCN Guidelines because this is done every year and I am very aware that its a great deal of work. So, thank you very much for that, Dr. Mohler, and thank your dear colleagues as well. Perhaps if there was one last thing which you would like to wish for that we might see in the next couple of years, could you tell us what that might be?

Dr. James Mohler – I would like to see all these tests that attempt to better stratify tumors in individual patients come to a fruition so that we can realize our goal of truly right sizing treatment so that people who need to be treated can be and those who don't need it, we could avoid these treatments because all of them, no matter how well done, have side effects.

Michael E Scott – I would concur with you and tell you I think that would be a wonderful thing. Priya?

Priya Menon – Dr. Mohler, thank you very much for being with us today. Mike, Tony, and Paul, thank you for

your participation and hope all of you will join us again for Cure Talk's next talk on prostate cancer, which is scheduled for March 19th. We will be discussing clinical trials to enroll in with Dr. Maha Hussain of the University of Michigan. Please visit our new website, curetalk.com, for information on our upcoming shows and the link for today's discussion will be sent via email to all the participants and we will be putting up a transcript of the show too on our website very soon. Thank you very much.

Michael E Scott – Thank you, everyone, for your time. I appreciate it.

Dr. James Mohler – Thank you.

Paul Carpenter – Thank you, Dr. Mohler.