Focal Laser Ablation in Treatment of Localized Prostate Cancer - A Developing Therapeutic Option

MRI-guided focal laser ablation of the prostate is a developing treatment option for patients with localized prostate cancer. We are talking to Dr. Ara Karamanian on this new treatment technique and its nuances. The panel discussion will include a brief background to the development of the technique, as well as touch upon aspects like, patients who are eligible for this treatment, side effects, complications that may occur, physicians who may have significant experience to perform this treatment etc.

Full Transcript: Priya Menon – Good evening and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks joining you from India on CureTalks' 116th episode. Today, we are talking about focal ablation of prostate for treatment of localized prostate cancer. Our prostate cancer talks are conducted in association with Prostate Cancer International and Prostate Cancer Foundation. Today's panel is talking to Dr. Ara Karamanian, a specialist in MRI-guided focal laser ablation of the prostate, which is a developing new form of treatment for prostate cancer. The panel will discuss the treatment technique in detail and cover categories of patients who are most appropriate candidates for this type of treatment, brief background of the development of the technique, number of physicians with significant experience, unknown side effects, and more.

Priya Menon – Co-host for the show is Mike Scott. Mike is Co-founder and President of Prostate Cancer International, a prostate cancer-specific and not-for-profit educational and informational organization based in Virginia. He is the Former Chairman of the Board of the National Organization for Rare Disorders and is a board member of the International Myeloma Foundation. Joining Mike on the panel are prostate cancer advocates, Tony Crispino, a 10-year survivor of advanced prostate cancer, in remission now, and working with the nation's top researchers as a patient advocate. Jan Manarite who is caregiver, widow, educator, and advocate for past 15 years. She is currently Executive VP of the Prostate Cancer International. Jim Dixstrom, Jim was diagnosed with prostate cancer in 2011. He underwent HIFU and has a current PSA of 0.4. A warm welcome to everyone to CureTalks. Before I hand over to Mike to begin with the discussion, I would like to remind all the people who have dialed in and who are listening to us online that we will be addressing questions sent in towards the end of the discussion. If you have a question you would like to ask, please press 1 on your keypads and we can bring you on air to ask them. You can also email your questions to priya@trialx.com or post the question on curetalks.com. With that, its over to Mike. Mike, you are on air.

Mike Scott – Thank you, Priya, and good evening, everyone, and good evening to you, Dr. Karamanian. I appreciate you taking the time to talk to us this evening. Thank you very much.

Dr. Ara Karamanian – Thank you for having me.

Mike Scott – Not at all. What I think we would like to do is give you about 15 minutes or so to give us some initial background on where you think people are in the use of focal laser ablation today and a sort of general overview dealing with the different types of FLA, the types of patients who you are seeing, and where we are in the development of this technique, which obviously has potential but obviously is missing a lot of features yet.

Dr. Ara Karamanian – Yes. That is definitely one of the criticisms of any emerging technology. You can't have long-term outcome data until its been done for a long time. So, but, that's obvious. So, let me explain sort of where the origin of this is, where the origin of MRI-guided focal laser ablation came from, and then how we got to where we are and where we look to be going. So, traditionally with any, when you do a biopsy of any organ looking for cancer, you use some sort of imaging guidance to see your target and use that to

direct a needle into that target. You wouldn't do a blind biopsy of the prostate…, of the breasts. You wouldn't do a blind biopsy of the lungs or you wouldn't do blind biopsy looking for liver cancer, so it is with image guidance. Unfortunately, up to very recently, we didn't have a good modality for image guidance where we can actually target a lesion in the prostate. There has been some work with ultrasound, but unfortunately, ultrasound, the sensitivity is extremely poor for clinically significant prostate cancer.

Dr. Ara Karamanian – Now, with the advent of prostate MRI and multiparametric MRI, we've improved tremendously in our ability to actually image the prostate and find lesions in the prostate. Its not perfect, but its really been a huge breakthrough and so the first step was to do MRI-guided biopsies where we can see a lesion often times missed on the TRUS biopsy and then put a biopsy needle directly into it in order to get a sample and there are many studies that show that especially after a negative TRUS biopsy, an MRI plus targeted biopsy leads to much better sensitivity for clinically significant prostate cancer than just a repeat blind TRUS biopsy. Blind TRUS biopsies are nontargeted, in the sense that they don't look to hit a particular lesion, but they are systematic and segmented in that they go through systematically through the prostate, but only a small portion of the prostate is sampled.

Dr. Ara Karamanian – There's MRI-guided focal laser ablation. There's also ultrasound or fusion-guided focal laser ablation. I want to make a little, a brief distinction here talking about the two guidance technologies. So, there's the guidance technology and then there is the actual ablation technology, the source of energy that causes tissue death and there is such a thing as MRI-guided HIFU. There is ultrasound-guided HIFU. There is MRI-guided focal laser ablation. There is ultrasound-guided focal laser ablation. MRI guidance has tremendous advantages, in that you can actually see the lesion directly with the MRI in real time. Also, MRI is able to measure temperature changes of the ablation tissue, of the tissue that you are targeting to try to avoid in real time as you turn on the laser and as you are doing the ablation and what we found is that in some men you need to increase the power of the laser to get it to the temperatures that you want. In other men, you don't want to turn the power of the laser on quite as high and that real time MRI feedback during the ablation helps us to do that…, helps us make those judgment calls and those would help to create a structure of the ablation in such a way that we are able to get up to the capsule without extending beyond it. That's clearly the goal when you are trying to destroy cancer that goes right up to the capsule without letting that ablations don't go beyond the capsule where it can hit the nerve.

Dr. Ara Karamanian – So, now, I would like to speak mainly about MRI-guided focal laser ablation, the reason being, there have been a couple studies with ultrasound or fusion-guided focal laser ablation. Unfortunately, the data on those patients…, the short-term data in terms of oncological control is rather poor when you have ultrasound-guided ablations. The current studies that have come out from the NIH and that have come out from the UCLA show that a very significant portion of those patients have residual cancer that was not effectively treated and…, but I would attribute that not so much to the laser but to the guidance technology. Its like sending a missile in to destroy a target. The missile might offer great explosion, but if the guidance doesn't take the missile to the target you are trying to hit, you are not going to destroy the target and MRI offers tremendous advantages in using it in real time during the ablation.

Mike Scott – If I may just quickly… If I may just quickly… So, what you are talking about is what someone else would describe as in-bore laser ablation. Correct? I just wanted to get that out because that's the term that I think people would have probably heard, but they may not have been fully aware what it meant.

Dr. Ara Karamanian – And I appreciate that clarification. I have seen at least one urologist describe MRI…, real time MRI imaging guidance, but he actually meant fusion guidance. So, its important to make the distinction regarding, from the perspective of a patient, to ask, am I actually in an MRI during the procedure or not. Because really you need those MRI images to be acquired during the procedure in order to improve that level of precision and so, there are two main approaches. One is the transrectal approach where a guide is placed through the rectum in order to angle directly towards the cancer. Another option is the transperineal approach, where the device is laid in the perineum which is sort of the bottom part of the pelvis and then guided into the prostate that way. Most practitioners are doing it transrectally. The distance to the lesion is shorter that way. It could be argued that its a little bit easier to put the laser fiber precisely where you want it

go, but that's…, its mainly…, truthfully, its mainly based on operator experience.

Dr. Ara Karamanian – There are some other techniques that are used to try to minimize side effects such as injecting a dilute amount of lidocaine or a fluid around the nerve in order to provide some thermal protection of the nerve so that when you ablate right up to the edge of the capsule, the fluid can absorb some of the extra heat that's coming off as opposed to the nerve absorbing it. When we do the ablation, the MRI in real time tells us what sort of temperature changes were created in the tissue and then it also…, at the end of the procedure during the contrast-enhanced MRI, it shows us whether or not we actually killed the region of tissue that we intended to. That's sort of the moment of truth, so to speak.

Currently, we have short-term data and I know its frustrating, believe me, I am.., I am looking forward to the long-term data being developed as well and I tell my…, I tell every potential patient that we don't have long-term data, showing, for example, improved overall survival versus, say, no treatment or comparing it to surgery. What we really need is a long-term trial that compares patients, you know, that are prospectively randomized into different treatment arms, such as surgery, radiation, MRI-guided focal laser ablation, HIFU. The thing is that with intermediate…, low and intermediate-risk prostate cancer, you really need 10 to 15 years to get good outcome or relevant outcome data. As a matter of fact, the ProtecT trial which did this with radiation and surgery just recently was…, just recently came out and you know how long we have been treating patients with radical prostatectomies and radiation therapy. Also, another argument along these lines is that the first data that really showed that surgery had improved survival compared to no treatment wasn't published… The first prospective study that looked at that wasn't published until 2005 and at that point, I am sure that there were many…, I have no…, I have no exact number, but I would guess that hundreds of thousands of radical prostatectomies had been performed prior to that sort of data being published and so with any new treatment, you have to look at the short-term data, look at it with some…, you know, and you have to look at it with some reservation and patients need to know that going into it so that they can make an informed decision themselves in terms of where they are placed.

Mike Scott – Again, if I may, I mean, I think this is…

Dr. Ara Karamanian – Sure.

Mike Scott – …this is one of the issues that we are very interested in. Clearly, you know, we all understand that nobody has got even five-year data yet, but certainly some people must have two-year data by now, which would give you some idea about the risk for side effects and the risk for complications at the time of treatment and I personally am disturbed that those data haven't been published by anybody because I know there are at least two physicians that could publish a series of data with that information.

Dr. Ara Karamanian – That's correct. Let me comment on this. So…, and first, let me talk about what has been published. So, the largest studies to date for MRI-guided focal laser ablation have come out of NYU and the University of Chicago and Chicago's was up to one year; NYU's, they did a biopsy at three months after the focal laser ablation procedure. Now, in terms of side effects, the side effects are…, if they are not…, if they don't occur within… Most of the side effects occur close to immediately in the perioperative period. We haven't really seen delayed side effects that occur an year or two years out and that's to be expected with this kind of technology. The safety profile for focal laser ablation… Again, there have been multiple studies that have looked at the safety profile which showed that it has a fantastic safety profile, especially compared to the more traditional forms of treatment for prostate cancer. The question in my mind is, what is the long-term oncological control data going to show? The short-term oncological control data, for example, in the study from NYU, I am sure that after doing MRI-guided re-biopsy of the lesion of ablation showed that 96% of the time there wasn't residual cancer in the area of ablation and that's probably…, that we are probably not going to be able to achieve those kind of results in the real world, but that gives you an initial sense of what the at least short-term efficacy of it is. University of Chicago, in their study, they did a biopsy at three months and then at twelve months and that showed not quite that level of control but also very good short-term control in the zone of ablation.

Mike Scott – Were these…, were these inpatients with known clinically significant disease or were these inpatients who we might be looking at today and saying, oh, they should be on active surveillance anyway.

Dr. Ara Karamanian – Well, the NYU paper may emphasize the point that 80% of the patients in the study would not fit the Johns Hopkins criteria for active surveillance.

Mike Scott – Okay.

Dr. Ara Karamanian – So, one… We should talk about active surveillance a bit because that really does play into this significantly. The problem… One of the big problems that we've had up to very recently is doing appropriate risk stratification. What do I mean by that? So, there is a very nice long-term study out of Johns Hopkins that showed that if you have Gleason 6 disease that really is Gleason 6 disease, your chance of dying from that are zero. There are a few scattered cases of Gleason 6 that have metastasized, but we are talking like much less than 0.1 or 1%. So, if it really is pure Gleason 6 disease, then, you know, do you really need to treat it, but then active surveillance is in those cases a very good option and the problem, though, is that… So, with the Johns Hopkins studies, they have the benefit of looking at all of these prostates, the whole gland, so they could determine that those Gleason 6 diagnoses really were Gleason 6 diagnoses.

Dr. Ara Karamanian – The problem in real life though is that you don't have a whole prostate to look at under the microscope when you need to counsel a patient regarding whether or not they should seek treatment and that again goes to the point of risk stratification. If you have a patient who undergoes a TRUS biopsy, comes back with a Gleason 6, how sure are you that that patient really only has Gleason 6 disease? There have been a variety of studies on this. Most of the data ranges between 30% and 70% in terms of patients who originally had a diagnosis of Gleason 6. What percentage of them were upgraded at surgery? What percentage of them actually had Gleason 7 disease but thought they only had Gleason 6 disease based on the TRUS biopsy. One of the arguments that urologists have made and, you know, with some degree of…, with some reason to it, is that, well, you have 6 on a TRUS biopsy and you actually have a 50% chance of having a Gleason 7, should we proceed with a radical prostatectomy? Now, that's led to a tremendous amount of over treatment and so one of the tools that we have been using to minimize that is MRI with fusion or an MRI in-bore biopsy in order to better risk stratify those patients. So, that way, we can have a higher degree of confidence that a patient who has a Gleason 6 diagnosis will only have Gleason 6 disease and then with greater confidence we can recommend active surveillance or they, you know, if they have a Gleason 6, the MRI shows something significant elsewhere in the prostate, get a targeted biopsy and let's look at that other sample and if that turns out to be, you know, a Gleason 4 + 3, well then, active surveillance wouldn't be appropriate and so, MRI has… Just to summarize, MRI has really advanced risk stratification and then focal treatment. Its…, its really enabled that.

Mike Scott – So, would I be wise in thinking that all of the patients who come to you asking about FLA, if they are…, if they have Gleason 7, you will do it assuming that its a relatively small amount of Gleason 7 and if its Gleason 6, you will say to them, well, let's…, let's make sure that you are really Gleason 7 and do a repeat biopsy under MRI guidance of some type.

Dr. Ara Karamanian – Well, it gets a little bit complicated. If a patient wants to…, a lot of it…, also to give consideration, a lot of it comes down to patient preferences. I can make my recommendations, but the decisions really come down to the patient. So, if I have a patient who has a Gleason 6, if that small volume on TRUS, get some MRI; the MRI is negative, I'll definitely recommend active surveillance. If the patient has a small volume or has a Gleason 6 on TRUS biopsy gets the MRI and the MRI shows a lesion that corresponds to the Gleason 6 seen on pathology, then active surveillance might be a very good…, could be a very good option for you, we should just talk about it and if they say that, you know, they really would like to…, active surveillance is a good option for them and that's what they would like, I look at the pathology and see if it matches up with the MRI. If it matches up and the MRI isn't too suspicious, you know, okay, let's leave it alone, get a repeat PSA, MRI, you know, in an year. If the MRI looks like its more suspicious than the pathology with…, then the pathology results from the TRUS biopsy would indicate, then I'll tell them, you know, we should proceed with an image-guided biopsy and I would recommend fusion or in-bore depending

on whether or not I think the fusion biopsy would be able to hit that lesion because there is some mis-registration with fusion versus in-bore biopsy.

Mike Scott – So, that…, that would mean patient with a PI-RADS score of 3, right, or higher, right?

Dr. Ara Karamanian – So, PI-RADS… It would definitely be 3 or higher, but it gets a little bit more complicated than that. PI-RADS really is a simplification of findings.

Mike Scott – Sure.

Dr. Ara Karamanian – Now, if a patient…Let's say a patient comes with a Gleason 3 + 4, that's 30% Gleason 4 and has, you know, 1 cm of length on the biopsy and has a concordant MRI lesion and it all fits together appropriately, then I'll offer them MRI-guided focal laser ablation. There are patients who have a Gleason 6 disease and tell me, look, I need treatment. I cannot go without treatment, you know, and I'll push active surveillance, but patients will push back and, you know, one of my patients recently told me, look, if you don't do focal laser ablation, I am going to go have surgery. You know, I can't leave that inside of me. Then, in those patients, I will agree to do MRI-guided focal laser ablation. So, let's maybe we should move on to talk about what patients are good candidates for focal laser ablation.

Mike Scott – Sure.

Dr. Ara Karamanian – So, if you have a…, if…, there is the ideal patient, I love it when I get these ones because its straightforward, technically easy and, you know, we have noticed in that we get good oncological control on these patients. An 8-mm single focus of Gleason 7 that has a good amount of distance between the neurovascular bundle and the edge of the lesion by a good amount of distance, I'd say, maybe a centimeter, those cases…, those patients are fantastic candidates, especially if the quality of the MRI is great and there isn't much confounding on the rest of the prostate. If the rest of the prostate looks clear and we can see things clearly on the MRI, I love taking care of those…, those little guys. Now, you can…, you can also ablate two separate foci, maybe 3, that's pushing it. Beyond that, or if there is diffuse disease, then I tell patients that they are not good candidates for focal laser ablation and obviously, I talk to all patients about a variety of alternatives, but then I would… With patients who have diffuse disease or really tremendous multifocal disease, I would decline to do a focal laser ablation.

Mike Scott – When you get a patient with two foci like that, are you more comfortable if they are both in one lobe of the prostate or both in one quadrant of the prostate? In other words, how… We obviously worry that this can be disseminated disease even though it is multifocal disease even though one can only see one or two small foci? How much comfort do you get from that sort of…, the positioning of two foci as opposed to one?

Dr. Ara Karamanian – Sure. So, if they are right next to each other, then I take out that whole area. If they are separate from each other, then I take out the one with plus margin, I take out the other one plus a margin. Its technically little bit easier to do them if they are next to each other, but…, but either way, it doesn't make a tremendous difference whether they are in separate lobes or if they are right next to each other, so long as their morphology, the size, the characteristics of the lesions are favorable, then it doesn't make a tremendous difference whether they are in one lobe or two lobes. The only… The issue does come in where I have seen unfortunately whether the lesion in the peripheral zone next to the neurovascular bundle, one on each side, and that significantly increases the risk of having sexual side effects. If you have to ablate right up to both nerves, your risk for sexual side effects does go up and that's what becomes an issue.

Mark Scott – Would you be usually be able to tell patients beforehand that that might be a problem?

Dr. Ara Karamanian – Always.

Mike Scott – Okay. Thank you.

Dr. Ara Karamanian – Sure. Let me just briefly talk about…, just as a clarification point. There is GreenLight laser for prostate that's completely different. GreenLight laser is used through the urethra, goes into the penis, goes to the prostate with a camera and the urologist cuts out chunks of prostate tissue in order to improve the symptoms of BPH. That's completely different than MRI-guided focal laser ablation for prostate cancer.

Mike Scott – So to summarize, basically what you are telling us, I think, is that by doing in-bore FLA, you are able to help the patient by using up what you believe to be a less invasive technique, that as far as you are aware, the short-term outcomes are pretty good from those patients, but clearly we are going to need long-term data and I get the impression you are saying that you believe that the in-bore technique is a great deal more effective than TRUS MRI fusion-guided FLA. In short, that's summary.

Dr. Ara Karamanian – Yes. Tremendously more effective because you can target lesion directly, measure temperature changes as you are doing the ablation, and you can do a post…, a post treatment MRI that's contrast enhanced to see the effectiveness of the ablation itself directly.

Mike Scott – So, the language that people used to talk about techniques that are in this stage of evolution is obviously important because, as we will currently be classifying this technique I believe is experimental, people like me tend to use the word investigational. I don't think anybody is going to be saying that that, you know, this is a fully validated way to treat prostate cancer yet, but certainly its very attractive to a lot of men because they think of it as lumpectomy or the equivalent of lumpectomy for prostate cancer and I worry about… I don't mean this unkindly, but I worry about, you know, the skill levels of the people who may be offering this at the moment and how a patient is able to get some clarity about that. I mean, for example, how many patients have you personally treated this way as yet?

Dr. Ara Karamanian – Sure. 42. And I know that's not a, that's not a tremendous number like 500 is, but, you know, I did complete a fellowship in interventional radiology and, you know, I've done cryoablations for renal cancers, microwave ablations for liver cancers. I have done easily over a thousand types of…, a thousand interventional radiology procedures and so…, and one of the benefits of the MRI-guided is it gives you very real time feedback in terms of the quality of the work that you are doing. So, if you are a good prostate diagnostic radiologist and can see what you are able to accomplish or what you may not have done as well as you would have liked to, if you are able to see that immediately, then that gives you real time feedback in order to accelerate your understanding and skill level much more quickly. I…, you know, the…, the people who are doing this at volume currently are, you know, it takes a great deal of skill to be able to do this well and so I do understand the reservations of, you know, being a new technique, I mean, look, if you go to… If a patient goes…, I wouldn't hesitate to have a patient go to whether its Dr. Walser or Dr. Feller or Dr. Sperling or to myself, patient is going to have… I believe that the patient… I would feel comfortable seeing patients with any of those practitioners for this.

Mike Scott – And…, I mean, my understanding is nobody has done 500 patients as yet. I mean, you know, in other words, my understanding was Dr. Walser might have done a couple of hundred himself by now. Is that about right?

Dr. Ara Karamanian – Dr. Walser has done roughly around 220 plus or minus 10 or 15. Dr. Sperling reports that he has done more than 500. Dr. Feller in California, I don't know the exact number that he has done, but its definitely over a hundred.

Mike Scott – Okay. So, Jim, I know you had some questions about this because you've talked to patients who have had problems after FLA. So, perhaps, you have got a couple of questions for Dr. Karamanian?

Jim Dixstrom – Yeah, certainly. Dr. Karamanian, you did a great job of explaining all those to people who really don't know the intricacies like me, me being a HIFU guy, but what I am hearing from a patient's point of view and looking at the logs, there's a problem with…., lot of it is likely… I mean people who misread the MRI may misread the targeted area that's the dark spot and they treat that and they miss tissue and they

have missed… I'd like to know from you too after I am done here, I have two questions, how much…, how often are people… How often are people re-treated because there was tissue missed in the original MRI, #1? What percentage of patients for these gentlemen, these doctors you worked with, had resections because that is another issue. There have been urologists who all of a sudden get this patient in their office, who has infection from an FLA and the person treating it, the FLA doctor wasn't prepared for the long term dealing with that patient and their business. There has also been a…. I don't know this for a fact, but I have heard complaints of recurrence and I have also heard concerns about damage to the tissue wall. So, these are areas from a patient's point of view that I personally heard and I am not an expert enough to explain it like you are.

Dr. Ara Karamanian – And I appreciate those questions. I am…, I am going to try to address them one by one, but if I forget one, please do remind me so I address that one as well. So, in terms of infection, now… If I may, let me make one comment to address a previous question from my…, a little bit earlier and tie that into this as well. So, I trained with Dr. Walser at University of Texas Medical Branch and we do have data that, that we are looking to publish within, you know, over the next six months that will add, you know, more patients to the…, to the knowledge database in the literature. One of the problems that we have had is that its…, its very hard to… The company that makes the laser really hasn't supported this at all in the field of prostate and so all of the efforts really falls on to us to try to compile all this and it takes a tremendous amount of work in order to do this in a rigorous manner and so we are looking to get that data published within hopefully the next six months or so, so stay tuned, but…, and I am going to speak to some of our experiences, although the data hasn't been published yet. So, I wanted to mention that. So…, and…, so, you know where I am coming from when I address some of your questions.

Dr. Ara Karamanian – So, in terms of infection, we have actually found that with focal laser ablation, there is less of a risk of serious infection than a TRUS biopsy. I am not ready to quote exact numbers for you yet, but and I think there is a good reason why that is intuitively. So, when you put…, yes, you use the transrectal approach except for University of Chicago uses a transperineal approach, everybody else, I am glad uses a transrectal approach. Yes, it does use that same transrectal approach that has a risk of infection associated with it. Some of the things we do to minimize those risks are we provide enemas. We have an enema that you can provide the morning of the procedure, do antibiotic coverage, but fundamentally one of the main differences with an FLA versus a TRUS biopsy or a prostate biopsy is that one, you imagine you are taking that tiny laser fiber, inserting it through the rectum into the prostate and you drag some bacteria with it, but what happens when you turn on that laser and it reaches 60 degree Celsius or higher, often 60 is sort of one of the cutoffs we use, but usually the temperature gets up to about 80 degree Celsius. That bacteria won't survive 80 degree Celsius. Now, what can happen though is you can immediately kill that tissue and the bacteria with it, but as the tissue is getting absorbed from the body; any time you have tissue that's not vascularized, that's not viable tissue, its at risk of getting infected and so we have seen some delayed infections that come from focal laser ablation. We haven't… In…, in my experience and to my knowledge, I am not aware of a patient who has needed to be hospitalized for infection after FLA. Its possible that there is one out there or its possible that there are couple out there that I am not aware of, but even…, even if the…, let's say, I am just making up a number.

Dr. Ara Karamanian – Let's say, we have two patients who needed to be hospitalized for an infection after focal laser ablation, that would still put the number less than TRUS biopsies. Now, there are patients who do…. Now, that's sepsis. That's a patient who has a very serious infection after focal laser ablation. There are patients who do develop infections that are less significant than sepsis and today, all the ones that I am aware of have been successfully treated with oral antibiotics. Regarding the practitioner managing a patient who has an infection, I mean absolutely, the physician who does the procedure should be able to provide that sort of longitudinal care. That sort of… That is one of the pieces of core training for me as an interventional radiologist, to be able to…, not just to be a technician but to see the patient, evaluate them, understand all the different facets of the different treatment modalities, be able to counsel the patient on those in order to explain the risks, benefits, and alternatives of the treatment that we are offering and then to be able to manage your own complications afterwards. Now, there are…, it can become a challenge when, for example, a patient flies back to, you know…, let's say a patient comes to Texas, gets treated here, flies back,

you know, to the state that they are from, managing that infection across, you know, a long distance, it would probably be better in those cases for a local physician to prescribe the antibiotics in consultation with the physician who did the procedure, but the physician who did the procedure should definitely be part of a team who is taking care of that patient and if the patient is local and if they are responding appropriately to the antibiotic therapy, then there is no need to get somebody else involved. If, for example, though there is a serious complication and I am just speaking in general now, if there is a serious complication, then its appropriate to bring in physicians of different specialties who can provide advanced sub-specialty care. Did I sort of address your questions?

Jim Dixstrom – Yeah, you did. I just think there are gaps. I don't want to be critical here, but, you know, you can hear from what professionals tell you, then we go and see the people's actual comments on multiple sites and, you know, it brings to question long-term credibility and, of course, HIFU has compromised credibility so far, be it long term and so there's FLA in its infancy, but there is also pilot error and I don't mean to be rude by saying this, but there are guys who just say their doctors screwed up because there is a very steep learning curve in your business with FLA or HIFU or da Vinci. So, just from my point of view, I am trying to meander through the parts about, this isn't just about you as a professional.

Dr. Ara Karamanian – Of course.

Jim Dixstrom – This is about your industry laterally. These are the physicians who have the same passion for excellence that you do and we have already seen, of course, that that is compromised in some people's practices. So, again, I just… There's too many…, like Mike has said, there are too many incomplete things here that make it compelling. I am also troubled by some of these patients that are treated, they don't need to be and you know that you have already shared… They are good candidates for active surveillance, but they want to just get rid of the cancer and that's happening with over treatment in multiple treatments across the country here, which is troubling, but FLA is so controlling for us, but how do you deal with a tiny thread that you are going to miss? The MRI, if you read, not you read, somebody else doesn't know how to read the MRI, so we miss a tiny thread of tissue, they may have to get re-treated again. How often does that happen?

Dr. Ara Karamanian – Well, I can tell you that before… Let me tie this in as well to a different…, another concept because I think its very relevant here. MRI-guided procedures should really, in my opinion, be done with those who have advanced training in using advanced imaging modalities to do procedures and that really is interventional radiologists and one of the big advantages that an interventional radiologist can bring to the table, who is also a very good prostate imager, is they can look at the MRIs themselves and see subtle nuances that aren't necessarily going to be reported or even seen by somebody who doesn't read a whole lot of prostate MRIs or isn't, you know, very experienced in prostate MRI and so, I take full responsibility. I review every MRI very carefully before I would consider doing an MRI-guided focal laser ablation on the patient. Believe me, I do not…, I do not rely on the reports from other physicians before I do this and its the same thing before I…, before when I would do like a microwave ablation for a liver or chemo embolization for liver cancer. You have to review the images yourself and really understand what it is you are seeing, what it is you are treating. There is no substitute for that and so its incumbent upon the treating physician to be able to do that.

Mike Scott – Is there any… If I may, is there any discussion going on between the societies about what the skill levels and qualifications should be for people who are practicing this sort of technique? I mean I realize this is always very complicated, but I mean in the end, its the profession that has to take responsibility for the quality of the practice.

Dr. Ara Karamanian – Well, its a yes and no. Its a little more complicated clinically. So, by the way, first of all, there was a meeting yesterday in Chicago that I was happy to be a part of, where some of us who perform MRI-guided focal laser ablation, you know, met and discussed some of the issues that are facing…, that are facing with technology. So, the… I spoke to the company that makes the laser fiber and I asked one of their representatives if there is somebody who, let's say, they have never done a focal laser ablation case

before. Let's say they have done two. You know, would…, would you sell them the equipment to do this and they said, yes, they would. I…, you know, for me that's…, that's frustrating because you want to have quality controlled there and only allow people who have demonstrated a high skill level in operating to be able to do this. Sadly, you know as a physician I have also seen surgeons who operate at low skill levels, you know, hurt a number of patients. Unfortunately, there isn't a good mechanism to be able to prevent people who, you know, who is going to play judge here, you know, who, you know, how do you…, how do you begin to set up that sort of regulatory system.

Mike Scott – Oh, no. I understand. I mean, it is one of the things that I always say to all patients, I mean if every surgeon has to do radical prostatectomy and every interventional radiologist who wants to practice FLA, is he obligated to do his first FLA on somebody. This is a…., this is a constant problem, but I do think, you know, we…, we…, there is an obligation on us all to try to help to give guidance as to what is acceptable in terms of the training and the practice using these techniques. Now, I don't want to delay this because I want to move on. Tony, do you think there is any hope of anybody actually being able to do randomized trials for this kind of thing?

Tony Crispino – No. I think that Dr. Karamanian pointed out very…, very clearly that doing comparative trials from the different modalities that are out there are going to be long term. They are going to be very expensive, they are going to be very difficult to accomplish. If there is a way to do a clinical trial, I think that could be used well with a subset, like you call secondary endpoints, would be to go ahead and take a patient who's made a decision that they are going to have surgery, that its their decision to go ahead and have surgery and possibly due to procedure ahead of that surgery so that you can gauge what was seen in the MRI versus what was seen in the actual prostate, total prostate biopsy. I think that doctor would probably agree with that. By the way, hi again, Dr. Karamanian. You and I spoke for over an hour about this in early September, really enjoyed all the paperwork you sent me on this, but that would be my suggestion if we are going to see a clinical trial on this, its going to have to go in a direction of maybe a subset trial to which this procedure can be piggybacked on to it to compare the MRI of efficacy versus the actual…, actual disease in the prostate. Your thoughts, doctor?

Dr. Ara Karamanian – I think that's brilliant. I just wish I could get Medtronic to pay for that kind of study, you know. I would love to do that. I would…., that would… I mean, I can't even begin to tell you how much I would love to be able to do that kind of study. The problem is, I mean, these things are expensive, you know. How do you get… NIH funding has really tightened up these last several years. Its…, its hard to get funding for this kind of study, but I think that would be fantastic now, but, you know, what's going to happen is you are going to have… Even after that kind of study, you are going to say, okay, well, there is no…, we don't see any clinically significant prostate cancer left, but does that really mean that the patient is going to live longer? Well, again, you still need a 15-year outcome data and there are still going to be people who criticize it, but there have been some studies that show that there's…, that…, patients who are already going to undergo radical prostatectomy who did undergo focal laser ablation but just to test the ablation modality, it did show that there is confluence…, confluent ablation, confluent depth in the zone of ablation and so that's encouraging. The issue then is going to go back to the multifocality question. May I make a few comments about the multifocality question?

Mike Scott – Well, I'd like…, I'd love to do that, but we've got one more person. I want to see if she has any questions and then I want to see if we can get some of the questions in from some of the people on the line.

Dr. Ara Karamanian – Sure.

Mike Scott – So, Jan, do you have a quick question?

Jan Manarite – I do. You know, I think for the listeners, patients listening, I think its important to talk quickly about cost and the fact that this is probably not covered by insurance. So, there's two ways, if I am not mistaken, that you can access focal laser ablation or most focal therapies, is #1, paying for cash. If I understand correct, its…, is it 20,000 or more, Dr. Karamanian?

Dr. Ara Karamanian – Yes, I have seen 20,000 to 32,000 being the range.

Jan Manarite – Okay. So, certainly that's something that you need to understand and ask upfront, but the second place would be actually in a clinical trial and I did look online and I found three right now, one is NIH, one is at Mayo Clinic, and one is at Indian Wells with Dr. Feller. So, I wonder if that's even a safer setting you would get better monitoring, I don't know, just a thought, but I think its important to understand its not covered by insurance. So, the way you are going to access it is paying a large amount of cash or finding a clinical trial.

Dr. Ara Karamanian – Well, let me comment on that. So, first the NIH trial is with fusion, not MRI guidance.

Jan Manarite – Okay.

Dr. Ara Karamanian – And… There are reasons why they are trying to demonstrate this with fusion guidance, but again I would caution anybody from doing fusion-guided FLA. The outcome data has been bad and with good reason.

Jan Manarite – Okay.

Dr. Ara Karamanian – And then the Indian…, by the way Dr. Feller with Indian Wells, he is definitely doing the most rigorous clinical study on focal laser ablation where he does an MRI-guided biopsy before and after every patient who is getting…., who is undergoing FLA, but the trial isn't funded and so patients still have to pay out of pocket and I am not sure about the Mayo Clinic also, but I believe that the patients also have to pay out of pocket. So, that's how it works.

Jan Manarite – So, they should ask even though its a trial.

Dr. Ara Karamanian – Yes.

Jan Manarite – They should ask. Okay. That's helpful.

Mike Scott – Okay. So, what I would like to do now is take a few minutes and hand this back to Priya to see if she has got questions from the audience for Dr. Karamanian. I know…, I know there were a lot of things that you went through, of course, but we would like to see what we can do for the patients who are on the line and have questions to ask you. Priya, would you like to take over again?

Priya Menon – Thank you, Mike. We have been receiving questions on our website actually, Dr. Karamanian. So, I'll just quickly go through them. Some of them you have already answered through our discussion. The first one is, given that one has a 3-Tesla MRI showing the lesion, does it make sense to do an FLA without a biopsy first or to do the biopsy at the same time and get the results a few days later or is the biopsy result important prior to the FLA? That's from Ed.

Dr. Ara Karamanian – Sure. Its important to have the biopsy results prior to the FLA and the reason is…, there are many reasons. So, let's say that it really turns out to be a Gleason's…, a low volume Gleason 6 or even a moderate volume Gleason 6, but only Gleason 6. Then, the patient needs to, you know, not while they are on a procedural table and sedated, but while they have…, their thoughts clear and collected and they can think clearly and really evaluate, okay, do I want a treatment or do I want to just stay on active surveillance. That's…, they need to be able to make that decision and what you can do if you biopsy and ablate immediately. Another thing is that, let's say it turns out to be a Gleason 9 and the patient is, you know, 55 and has a life expectancy apart from the prostate cancer of more than 30 years. That's going to be a patient who should undergo more aggressive therapy and so its important to be able to tailor the treatment to the patient which you can't do until you have the pathology results.

Mike Scott – So, are you telling me you would never do this on a patient with a Gleason 9?

Dr. Ara Karamanian – I would never do this on a young patient with a Gleason 9 who.., who has a long life expectancy. Now, when I say never, I mean given the current data or 20 years from now, I might depending on what the data shows but…., and the reason is that Gleason 9 has Gleason 5…, Gleason component 5 inside of it and those cancers can really spread in a way that you can't see well with MRI and so if I don't feel comfortable that I can ablate the index lesion plus the margin, then I don't want to…, I don't want to treat the patient. High-risk disease needs aggressive therapy, not intermediately aggressive therapy like FLA or not no therapy like active surveillance. Aggressive disease needs aggressive therapy.

Mike Scott – Thank you. Next question, Priya.

Priya Menon – Thank you, doctor. The next… Yeah. The next one is, what is the accuracy of 3 TMp MRI for lesion size? How small a lesion can be detected?

Dr. Ara Karamanian – Well, so that goes… An important part of that is…, answer that question is the quality of the imaging at the center. So, the better the quality of the imaging, the smaller the lesions you can see, but less than 5 mm, its tough for a 3T multiparametric MRI to pick up a lesion that's less than 5 mm. Now, having said that, what are the chances that a lesion that's less than 5 mm is going to actually become clinical disease. Well, maybe at some point in the future, but we would be able to pick it up as it grows. So, there are small cancers and definitely small Gleason 6's that 3TMp MRI will miss, but I would argue, if a patient has a 3-mm…, a 3-mm Gleason 6, you shouldn't even treat it. So, who cares if you don't see it? If they have, you know, 3-mm Gleason 7 cancer, its probably going to grow to the point where you can see it on the MRI before…, before anything bad happens. Now, having said that, we do know that, you know, MRI for the prostate is not 100%, but there is only one test that's really 100% for prostate cancer and that's a radical prostatectomy, but obviously that's far and way overkills the diagnostic modality. So, one of the great things about multiparametric MRI is it tends to miss clinically insignificant cancers and its very sensitive for clinically significant cancers, but if the MRI is negative and a patient is in the high-risk clinical scenario, they should still undergo blind TRUS biopsy.

Priya Menon – Thank you, doctor. Now, there's another question. What role does PSA testing play post FLA? Also, what type of increase should be expected over time?

Dr. Ara Karamanian – Sure. So, what we found is that the PSA drops at the first measurement post FLA which is usually done at six months and then it usually stabilizes at about a year and then between year 1 and year 2. Now, if it… What we found is that when it drops to less than 30% of its original value, the chances of having residual recurrent disease is extremely low. When it…, when it drops at 50% of the original level, then there is still a very low risk of residual disease. What we do is we use PSA in order to track…, I mean just like you use PSA after radiation or after surgery, if it starts to go up and if it goes above the pre-ablation number, then we're worried whether or not we see anything on the MRI.

Priya Menon – Thank you, doctor. Next question is, what are the chances of patients losing sexual function as result of this procedure and when there is loss, other ways to recover it, yeah?

Dr. Ara Karamanian – Sure. So, if there is bilateral disease where its going right up to the neurovascular bundle on each side and the nerve is right against the capsule, you know, then the patients are at a higher risk of having erectile dysfunction. Overall, the risk of it developing impotence from this procedure is less than 10%. With patients who have cancer that's unilateral and not going right up against the nerve, the chance of having any effect on sexual function is going to be very low. Now, let me rephrase it. Having significant impact on sexual function is going to be…, the risk is very low in those patients. We do know of a phenomenon where the nerve can sort of be stunned and then the patients will regain sexual…, will have a drop in their erectile function immediately after the procedure and then over the course of a few months it will come back. So, let me try to be little more clear. When a patient has sexual problems after focal laser ablation, its…, its immediately apparent within the few weeks after the procedure. It does tend to come back to varying degrees over the course of a year or two with patients, but again that's going to be the small minority of patients who deal with significant sexual function…, significant sexual problems after focal laser

ablation. One of the things we do is we also supplement patients with Cialis to try to improve that function as needed.

Mike Scott – Is that an age-related effect or is it more real, sort of indicative of heightened risk?

Dr. Ara Karamanian – I am sorry, say that again.

Mike Scott – Is that in any way related to the patient's age or anything else, I mean in other words, do you have any ideas about why some patients are at greater risk than others?

Dr. Ara Karamanian – Yes. So, for cancers that are right next to the neurovascular bundle where you are ablating right up to the nerve, that's a risk factor. Having bilateral disease in a problematic area is a risk factor and yes, older patients tend to have lower baseline sexual erectile function and so, the lower a patient is starting off, the more at risk that a little bit of a hit will have a significant impact in terms of sexual function.

Mike Scott – Thank you.

Dr. Ara Karamanian – So, you know, a 55-year-old who has fantastic sexual function and you singe the nerve a little bit, if you irritate the nerve a little bit, often times wouldn't notice any impact.

Mike Scott – So, I don't know if you think we have time for one more question, Priya.

Priya Menon – I think that's all the questions that we have from the listeners as of now…

Mike Scott – Okay.

Priya Menon – …and, Mike, if you have a question, you do have a minute more. Yeah.

Mike Scott – No, I…, I…, I think I…., I just want to thank Dr. Karamanian for his time. I think this has been a very helpful introduction for lot of people. We all understand that new techniques take time to prove themselves and I…, I think I have said to you in a couple of emails. I encourage you to encourage your colleagues to publish as much as they can, as fast as they can because I think that will only help everybody to understand what the opportunities are here.

Dr. Ara Karamanian – I agree a 100% and believe me, I am making efforts along those… I am trying to make it happen.

Mike Scott – Thank you.

Priya Menon – Thank you, Mike. Before we wrap up this session, I would like to inform everybody that Prostate Cancer International is conducting a one-day conference on March 4th for patients and caregivers. Both Mike and Jan will be there moderating sessions. Jan would like to say something on this.

Jan Manarite – Yes. Its in Southwest Florida and it should be a great conference where the intention is to just serve people and help them. There will be a lot of Q & A, a lot of networking, and I think it will be a great conference. So, we are asking for a 25-dollar donation, but if you don't have the 25 dollars, you get in free. We won't turn anybody away.

Priya Menon – That's great! Thank you. Thank you, Dr. Karamanian. It was a great informative session, as Mike just mentioned, and I hope this treatment picks up soon and helps lot of people. Mike, Tony, Jim, and Jan, thanks so much for your participation and the talk is going to be put up on CureTalks' website for playback along with its transcript. Please visit curetalks.com for details on our upcoming talks. Thank you, everyone.

Jan Manarite – Thank you.

Mike Scott – Thank you very much, Priya. Good night!

Dr. Ara Karamanian – Thank you.

Priya Menon – Bye, bye.