HIFU & Focal Therapy for Prostate Cancer

“Decades after lumpectomy became a standard option for women with breast cancer, men are seeking a similarly targeted approach to prostate cancer, one that gets rid of the tumor while preserving the organ. Now, an array of technologies is enabling doctors to visualize and zap away prostate malignancies. Tissue is destroyed, or “”ablated,”” by energy from lasers, microwaves, extreme cold, or ultrasound. The presumed – but not yet FDA approved – advantage of focused ablation is less collateral damage. In other words, less incontinence and impotence. Tune into learn more about HIFU and Focal Therapy from Prof. Emberton.

Full Transcript:

Priya Menon : Good afternoon, everyone, and welcome to the Cure Panel Talk Show. I am Priya Menon, Scientific Media Editor of Cure Talk, Cure Panel, joining you from India and I welcome all of you for a discussion on prostate cancer. All Cure Panel shows on prostate cancer are conducted in association with the Prostate Cancer International and Prostate Cancer Foundation. This is the fourth time we are discussing prostate cancer on the Cure Panel platform and we have had over 10,000 people listen to our prostate cancer shows. Our previous show had Dr. Bruce J. Roth of Washington University talk about hormone therapy for advanced prostate cancer. Today, we have with us a very distinguished guest, Professor Mark Emberton of University College London Hospital. Mr. Emberton is Director of the Division of Surgery and Interventional Science at University College, London. He is also UCL Partners’ Pathway Director for urological oncology for London Cancer, a provider network serving 4 million people that live north of the river Thames in London. He is the Honorary Clinical Director of the Clinical Effectiveness Unit at the Royal College of Surgeons of England. As Professor of Interventional Oncology at UCL, he leads a clinical innovation team that majors in experimental medicine by combining bio-engineering and nanotechnology with early phase trials in men with prostate cancer. He is an active researcher, lectures widely, and had published over 200 peer reviewed articles in numerous scientific journals. Mark Emberton is a Founding Partner of London Urology Associates. He is also a Trustee of the charity, Prostate Action. Welcome to the show, Professor.

Dr. Emberton : Hello. Greetings from London!

Priya Menon : My co-host for the show is Michael E. Scott. Mike is Co-founder and President, Prostate Cancer International, a prostate cancer-specific, not-for-profit educational and informational organization based in Virginia. Mike is an Executive Vice-President of Independence HealthCom Strategies Group, a privately held group of healthcare communications companies based in Philadelphia. He is also the current Chairman of the National Organization for Rare Diseases and a member of the Board of Directors of the International Myeloma Foundation. Mike, great to have you and welcome to the show.

Mike Scott : Hi, Priya. Thank you for the invitation and good afternoon, Mr. Emberton. How are you today?

Dr. Emberton : I am extremely well, extremely well. Looking forward to the discussion.

Mike Scott : So, perhaps you should…

Priya Menon : Supporting…

Mike Scott : Oh, I am sorry. You go ahead, Priya.

Priya Menon : Yeah. Yes. Yes. Thank you, Mike. Supporting Professor Emberton and Mike on the panel are experienced and knowledgeable prostate cancer survivors and advocates, Jim Wickstrom, Richard Davis,

and Allen Edel. I extend a hearty welcome to all panelists and to all our listeners. Today, we are discussing focal therapy and HIFU for prostate cancer. Decades after lumpectomy became a standard option for women with breast cancer, men are seeking a similarly targeted approach to prostate cancer, one that gets rid of the tumor while preserving the organ. This is sensible for many reasons, starting with the fact that the golf ball-sized gland is inaccessible. It lies deep into the pelvic cavity, surrounded by sensitive structures that are vital to sexual and urinary health. The urgency has never been greater. The PSA screening test once seen as a life-saving early detection tool is no longer recommended by health experts because too many men are being treated for cancer that left alone would not become life threatening. With the disease estimated to kill 30,000 American men a year, despite a 30% reduction in deaths since the PSA was introduced in the late 1980s and being urged to use an option men find nerve racking, that is monitor rather than treat early stage cancer hoping it doesn't grow. Targeted ablation is seen as a possible solution to this dilemma, at least for some patients.

On today's show, we will be learning more about different applications of HIFU, that is high-intensity focused ultrasound, and focal therapy, removal of tissues from only selected areas of the prostate in the management of early stage localized prostate cancer. I would like to remind all our listeners that we will be discussing questions sent in via email at the end of the show. With that, now I hand over to Mike to begin with the discussion. Mike, you are on air.

Mike Scott : Thank you, Priya. So, Dr. Emberton, perhaps you can spend a little time telling us about the basics of HIFU and other therapies of similar potential and how they can be used in focal therapy and one of the things I would particularly like you to delineate for us is where you start to draw lines between the patients who may be good candidates for active surveillance and those who, you know, will benefit from therapy and the issues that come up in your discussions with patients about this.

Dr. Emberton : Thanks. Well, that's a great, great starting point. So, I think its probably worth starting just reflecting on the last 100 years of treating prostate cancer since radical prostatectomy was first done in the beginning of the last century and all our treatments have been directed at the gland rather than the cancer because of our inability to localize the cancer within the prostate and that's the thing that's changed. So, what we are able to do is transition from an era where we were blind to cancer location to an era when we are not and its just worth reflecting what happened in other organ systems when that opportunity became evident and in urology, within my working lifetime, we transitioned from radical nephrectomy, removing the kidney in everybody with any tumor, small or large, to a much more individualized approach where some tumors we watch, some tumors we ablate, and where we can and in most patients today, we try and preserve as much kidney as possible in the knowledge that that benefits patients in the long term.

You know, before my time, the revolution happened in breast cancer and indeed if we look at all the solid organs around the body, its just the prostate that we insist on removing in totality because of our so-called inability to localize disease. And also interesting is that of all the tumors I have discussed and many had happened, prostate overall is the least lethal of them and so it should be possible if its possible in more lethal tumors like kidney cancer, which has a 50% overall five-year survival, it should be possible to do it in prostate cancer, which has, you know, a 90% to 95% ten-year survival in most of the studies that we have looked at and I think the opportunity really is a convergence of technology. Its the ability to localize the tumor with MRI and I think that's one technology now that is gaining enormous attention. The second technology is the ability to sample that area accurately and image registration, which is a kind of product to computational science is now fairly mature. There are 10 companies now offering MRI to ultrasound registration systems, something that the newer sections have been using for 5 to 10 years, but its just starting to come into urology and the third technology that was hitherto missing is now available, technology that allows us to place energy within small volumes of tissue and importantly preserve the structures between the release of that energy and the product of that energy, which is the focal point of treatment, and the HIFU is one example of that and there are many others that I am sure we will discuss.

So, those are the three things that have all really emerged in the last decade at slightly different times but are now all fairly mature to allow us to find therapeutic target, the cancer cells in the prostate and that is

essentially the background to this research question that we are asking. So, you know, can we do it and if we do it, can we preserve oncological efficacy? In other words, can we cure patients, stop them progressing and if we can, can we do so without decrement to their genitourinary function and we will talk about the results of some of the studies which tell us the extent to which we have achieved those goals, but I will stop that for now, just to see in which direction you want me to go to in terms of your questioning.

Mike Scott : I am perfectly happy for you to go right ahead. I think you set up the ground work just fine and I think the important thing is for you to give us a straightforward view of where you think we are at and then we will probably have detailed questions after that.

Dr. Emberton : Okay. So, I think… I think when you explain this to patients, the patients get it and very quickly because obviously they place high utility on the preservation of function and they appreciate that technology can allow us to have cancer as our target rather than the whole organ, which we do in the colon. In the bladder, urologists are very comfortable treating lesions, small lesions, when and as they occur and in the knowledge that they will recur because removing the bladder is such a catastrophe to the patient's quality of life, but urologists also recognize that there are some patients who need their bladder removed, who have particularly aggressive disease, disease that recurs or widespread disease and if we look at the breast, all women had mastectomy 30 to 40 years ago. Now only one-third of the women presenting with breast cancer require mastectomy, but there is still a group that do and they obviously widespread aggressive disease. So, it was said in the beginning that a tissue preserving or selective therapy for patients will not be for everybody and at the moment we are in the process of defining who it is that is most likely to benefit from such a treatment and there are several issues that are discussed when we have this discussion in public amongst urologists or with patient groups and certain themes and questions tend to emerge.

The first I think is that does tissue preservation matter and I think we know the answer to that and this is a side effect question. We don't need 15 to 20 years of followup to ascertain whether erections and continence is preserved and its now been several thousand patients treated in a focal manner, only a couple of hundred in formal registered prospective studies, but even in those couple of hundred who have been very, very carefully evaluated, there is no difference in baseline function prior to treatment and after treatment with respect to erections and urinary continence, which I think is a real revolution indicating quite emphatically that preserving tissue makes a difference and I think the reason it does make a difference is that most of the harms associated with therapy come not from treating the prostate itself but from damaging important structures that surround it and they include rectum, ureteric sphincter which is the muscle that we use to interrupt our urinary stream, the nerves that run just down the side of the prostate that mediate erections, the bladder neck that's important in ejaculation and also in continence in some men and also the bladder which can get affected by sometimes surgery and sometimes radiotherapy that can result in frequency and urgency and by limiting the harm, if you like, just to the cancer cells and the small area around it, all you treat is prostatic tissue, most hopefully prostate cancer cells, but obviously you have to place more margin and very little collateral damage occurs as a result and that's the reason I think why you can treat somebody with focal treatment and you can see them as we did several patients yesterday and you ask them about continence, its the same; you ask them about erections, its the same; you ask them even about their ejaculation and if not quite the same, its still present but slightly reduced in terms of volume and so those are the kind of outcomes that we are trying to create and I think now there is good evidence that you can do that by treating anything up to or less than half the prostate. So, that's that aspect.

I think the other thing that we know about definitely without any uncertainty is the safety profile in that also issues of toxicity can be derived early and we have enough patients in prospective trials and registries to know that the toxicity levels, in other words, the complications and the harms associated with therapy low. We have got comparative data now in the public domain in the new England Journal Of Medicine this year from the pivot study which shows that 20% of men are incontinent of urine and 70% to 80% men are impotent after surgery, twice as many as would be with surveillance. So, I think that's quite evident. What we don't know, of course, are the long-term oncological outcomes because as we have learned from other studies is that that requires probably 10 or certainly 15 years to derive in this medium risk group that I think and many others think are probably the ideal patients to receive this treatment and therefore, men who

choose to have this treatment have to do so without any certainty or long-term data just as the men who had radical prostatectomy in the 90s had to or radiotherapy in the 80s and that's obviously something that has to be shared with men.

We do have short-term data. Some would call it medium-term data. So, in other words, soldering the prostate after a given interval after an intervention and we can get freedom of disease, the various definitions that were slightly different, but they all try and confer some notions of freedom of disease and they vary depending on the study and the time frame. Between 82% and 94% of patients are free of disease, in short to medium terms which again compares very favorably with other treatments. Beyond that, we just have to wait and see.

The other kind of uncertainty area of debate and again this was alluded to earlier is who is the right recipient for focal treatment and this requires a conceptual change in thinking as well as defining a lower and upper threshold of risk and the conceptual change in thinking I think is probably the most difficult one and it relates to multifocality. We have learned, I think, recently or fairly recently that multifocality exists in all cancers, but the progression of the very small cancers is uncertain and the best kind of metaphor for this is a weather one, I think, is that predicting the weather a long way away from the time that you are predicting, is very, very difficult to do just as it is in cancer. In cells that look abnormal but can't be seen or felt or imaged, its very, very, very difficult to predict their time course and most do not progress and we have evidence for this in the thyroid, in the breast, in the bladder, and also I think in the prostate. Multifocality is dominated thinking because of the ways in which we randomly sample the prostate and that tends to pick up microscopic disease that cannot be seen and cannot be imaged and therefore is subclinical and that's been the part of all our life for decades and its very, very difficult to forget or not to incorporate in our thinking.

If you think about all other cancers, that's not done. What we do with all other cancers is either feel or image an abnormality and then interrogate that abnormal feeling or that abnormal image and that will be either an x-ray or something that you can feel or see. It might be a melanoma on the skin. It might be an abnormality on the kidney on ultrasound or in the liver on CT scan. You don't interrogate the whole organ. If you do, you find multifocal disease, but we don't do that and therefore we don't find it and the breast, I think, is an excellent example of that, in that you do a mammogram and you interrogate the abnormal bit of mammography or MRI or the palpable lesion, in other words the clinical phenotype, but you don't sample the rest even though breast cancer surgeons know that both the involved breast and the uninvolved breast are riddled with multifocal disease, but they don't seem to recur and they don't seem to progress and that has been nailed now with two articles, comparing whole breast radiotherapy with just irradiating the lesion. So, its not multifocality that causes recurrence. It is recurrence within the scar of the original excision and this multifocality issue comes up again and again and I think is the experimental side of the treatment and therefore we have to decide who is eligible for focal therapy. Is it men who have, let's say, disease in the top left hand corner of the prostate and no disease evident elsewhere and even if no disease is evident elsewhere, we know the disease will exist if we repeat the biopsies enough times or do we define a threshold disease above which we declare it to be significant and below which we ignore? Multifocal disease rise obviously if we use an imaging-based sampling strategy as we do in all other cancers, but for the time being, the lateral approach is what is being offered by many other commentators including Ian Thompson, who is arguing amongst others that the Gleason 3 + 3 that we call cancer isn't cancer at all and should be called something like idle, i-d-l-e, in the lesion of epithelial origin and if that were to happen, then we would get rid of most of the "multifocality" and we could concentrate on identifying and treating Gleason 4, Gleason 5 disease, because Gleason 3 is being relegated a a non-cancer. So, I am going to stop a second because I have covered quite a lot of ground and I have gone on for a bit, but I have tried to highlight the areas that tend to get discussed when this approach to therapy gets mentioned and this relates to case selection, it relates to oncological outcomes, and it relates to the difficult problem of multifocality. I will just take a pause there.

Mike Scott : Yeah. I think you have given us an excellent introduction. Thank you. I have a couple of some immediate followup questions. The first one relates to just how small a volume of tumor within the prostate, rather how small a volume of tissue we can treat focally at the moment…..and whether you think we are going

to be able to get too much smaller volumes than that? And the second one relates to patient selection in terms of other factors. Because one can do something it doesn't necessarily mean its the right thing to do and obviously co-morbidities and other factors need to be taken into account in deciding who to treat and that comes back to the question of how one does define a risky prostate cancer at all. In other words, you know, is true low-risk cancer really not cancer or is the patient's mindset about it in fact a key part of the decision process? So, I am interested in your comments on these two aspects.

Dr. Emberton : Great! So, let's do the lesser one first. So, the other thing that's happened in the last five years is an improvement in the precision of risk stratification. Urologists talk about half of my patients are upgraded to radical prostatectomy and what they are actually observing is imprecise risk stratification. What they are saying is that my ability to stratify the risk of the patient in front of me is wrong half of the time. Right? _____ all recognize and its a function of the TRUS biopsy which misses disease, misclassifies disease, you know, etc., etc. I think that's very well known about that one. If you have that degree of error, it is not unreasonable to overtreat it because if you don't overtreat it, you will undertreat it and therefore, the just-in-case approach stands up to, I think, reasonable scrutiny and that's been driving a lot of the whole gland approach to treatment. So, you have low-risk disease. So, as far as we can tell your PSA is 5.5 and you have got 1 mm of Gleason 3 + 3 in one core and 2 mm in the core next to it and we have repeated your biopsies and haven't found anything and now the urologist knows and will communicate the uncertainty to the patient that that allocation of low-risk status is insecure and therefore the patient may be encouraged to have prostatectomy just in case. What's happening there is the prostatectomy is serving as the kind of diagnostic test coupled with a therapeutic test which will be unnecessary in many cases and necessary in some because of the imprecision of the original test.

With imaging and the image-guided biopsies now, we have got to a stage where the upgrading of radical prostatectomy doesn't occur in 50% of the times. It doesn't occur at all. In fact, overall you get downgrading in 5% through technical reasons in the way that the Gleason is being derived. So, we are now in a position if you have an MRI before biopsy, which is again the minority of men get this and you have good image-guided sampling with or without registration systems, we can get to a 1:1 concordance with radical prostatectomy, which means we can mis-stratify patients with extraordinary precision and that gives us fantastic opportunity to not create a large number of men because we can be secure in the knowledge that they are low risk and probably have a 0.3, in other words, 100 times less the population risk of a prostate cancer-related death during the lifetime. We can identify men at high risk that we have previously overlooked and they might have multimodality therapy, including surgery plus or minus radiotherapy and chemotherapy, but we can also identify men with aggressive disease that is localized, we know they exist, with great precision and they, luckily for them, might be suitable for a selective ablation, have their cancer removed or their prostate _____ if you like, by having that cancer treated to go into a surveillance kind of algorithm where PSA and the MRI might be reapplied over an interval of time. So, that's how I see it playing out. I see the growth in active surveillance and in focal therapy and surgery possibly being used in areas that wasn't used before, so very well characterize patients who are non-metastatic, who will have multimodality therapy, who have particularly aggressive and bulky tumors and that picture on painting is one of personalized care or precision medicine where you respond to the disease in front of you with an appropriate treatment strategy that reflects the risk of the individual at the moment. The tragedy is that everybody gets treated the same, irrespective of grade, burden, multiplicity, location of tumor, if you don't go to the bother of finding out where it is and so I think that hopefully explains the mis-stratification issue, but you will have to remind me what the first question was now.

Mike Scott : The first question was how much tumor, what is the smallest volume of tumor tissue that … you can treat at the moment? How much more that you think we can get?

(Laughter)

Dr. Emberton : Great! So, I think at the moment we are really treating quadrants of tissue, so this is about 5 to 10 mL of tissue if you assume that the average prostate measures 30 to 40 cc. We are treating kind of blocks of 5 cc's now. We can treat less and some of the dose escalation studies that we have done using

photodynamic therapy, which combines laser and a photosensitizer required single fibers to be placed to measure the necrosis within the prostate and there we were getting very, very tiny radiuses of treatment around the needle, which I think from memory went to 3 to 5 mm around the needle. So, that would be about 1 cc core of tissue. Some of the new energy sources such as NanoKnife electroporation which uses electricity and is a non-thermal treatment and there are some bipolar needles that are being developed, that again could treat about 1 cc of tissue. Some of the newer cryotherapy needles, these so-called third generation needles, again treat and kind of create an ellipse, a little bit like a lollipop of tissue destruction with a very hard edge around them, again going for about 1 to 2 cc's of tissue. That does raise the question of when does the prostate cancer become significant? At what volume does the prostate cancer merit therapy and I think risk is conferred by volume. As it is in all other cancers, why should the prostate be different, but also by grade and of course volume and grade are very closely correlated. So, volume is not a bad indication. MRI can detect 0.5 cc lesions, which are about 8 mm across, very well indeed with very high sensitivity, very high positive predicted value. It can identify high-grade 0.2 cc lesions, again with similar levels of sensitivity, but much below that lesions will be systematically overlooked, which I think is probably a good thing because that's disease that probably doesn't need to be identified and treated.

Mike Scott : Great! So, now I am going to bring in the other panel members and I would ask them to…I will ask them to introduce themselves, say a little bit about themselves and then, you know, they have probably each got a couple of questions for you. We are going to begin with Jim Wickstrom, who was actually treated by HIFU. So, we consider him to be the expert on the panel. (Laughter).

Jim Wickstrom : Hi, there, Mark! I will avoid my first question about can we find any pictures of your famous sock collection on the internet (laughter) which I think is so expensive.

Dr. Emberton : Well, I am wearing purple today. Yeah.

Jim Wickstrom : Ah! My favorite color. Thank you. So, you know, its fantastic. I can't write fast enough in this discussion here, but, you know, I was a HIFU patient who_____ and I had a 565_____ PSA and a Gleason score of 6, but I had 9 out of 12 cores positive. So I really couldn't do active surveillance and that's when you_____ because when you have a doctor telling you that you should do radiation, who is selling radiation, and you have the surgeon telling you, "I think I have only spared 50% of my ____ I had red flags going up, so ultimately I did my research. I interviewed the FDA biomed engineer to find out about HIFU and I did my research by interviewing dozens and dozens of patients because all guys right ____ tell you stuff and that is why I learned so much that ultimately I did HIFU with Dr. Stephen Scionti out of Boston and I can't rave about how my procedure went and how happy I am, but again after interviewing so many patients that I have found that there was misdiagnosis and when you mentioned, I assume that what you are doing is something similar_____, which means you are diagnosing using an MRI before the biopsy, maybe fusing it to an ultrasound so you can actually create a 3D image of the tumor, to see where they did the biopsy makes so much sense and yet here in the US so many doctors really, I hate to use the word _____, but they are just not informed about what's out there, either due to costs or they have no research on it, but how… My question is how often is your facility doing MRIs first before you do biopsies?

Dr. Emberton : So, I think, I think… I think that that's just a great question. So, in our public facility _____ so free at the point of delivery, we have been offering MRI to every single patient with a high PSA prior to biopsy now for six or seven years. The same has happened in _____ and also _____ and that process is diffusing very rapidly throughout Europe and you are quite right, not quite as quickly in the US. I think the other… There is a kind of moral issue too. You know, if you speak to urologists, they will tell you that they would prefer to have an MRI before a biopsy because who wouldn't, because there's no harm, there's no radiation_____ 40 minutes of your time, but that will give you the opportunity to avoid a biopsy possibly or indeed to have a better biopsy if you need one. So, I think everything I said is contingent on location and that location is driven by MRI and verified by a targeted registered biopsy, you are quite correct. We don't use the _____ system. The _____ is an excellent system which is, you know, Canadian invented, US distributed and helps get the MRI information on to the ultrasound. There are about 10 companies now that will offer to sell you software which is largely a result of computational mathematics to allow that process to occur. We

use several of them. We are developing our own as many other units are. The key, the absolute key, is MRI prior to biopsy. You are quite correct.

Mike Scott : Thank you. (Pause) Should I go on?

Priya Menon : Yes, Mike.

Mike Scott : I keep losing Dr. Emberton. Am I the only person?

Dr. Emberton : No, I am here. I am just… I am waiting for that question.

Mike Scott : Okay. Jim! Do you have another question for Dr. Emberton?

Jim Wickstrom : Well, _____. I am fascinated by the implementation of the affordable care that is happening in the US and we have got some controversy here that is quite publicly known as physicians in physician groups, maybe urology-oncology groups, who choose to have the patients do MRI ____ for example and they are self-referred and so here we are in the system of the private enterprise here in the United States where patients aren't getting the true picture of what's best for their particular situation and yet you are running more of a socialized medicine, I believe, in the areas and we are able to do things the way you see best as opposed for the patients as opposed to the US. Do you see the US transitioning to a more patient-centered, consumer-based area or do you think that we are going to be floundering around in the US with patients not being able to figure out what's best for them because they believe they are individual doctors.

Dr. Emberton : I think this is very important. So, I think programs like this are critical and I think this will be driven by patients much in the way that lumpectomy was in women with breast cancer and men will have to insist and the market place will respond to accommodate that they have imaging prior to a biopsy. If you don't have… Yesterday was fascinating. We saw… I had an American physician with me who works out of Florida. He is a urologist who came with his radiologist to learn about what we are doing and they get to take back a lot of what we do back to Florida and we saw several patients who had… One patient had three biopsies before, all negative, rising PSA, 15 by the time I saw him and the patient afterwards had four previous biopsies done and the PSA was now 21. We did an MRI and they both had large anterior lesions which are T3a disease, in other words locally advanced disease and that PSA had been rising over the preceding five years and you can imagine the distress and the anger that they felt getting the same tests time and time again, that was never ever equipped to detect their disease and by the time we did detect the disease, it was probably not curable and so, you know, it won't take long for this message to get out there, especially that the test is widely available and can be applied. You don't have to buy this, you know. All hospitals have the scanner. Most private facilities have arrangements with local providers to provide MRI.

There are a few things that are stopping it in the States and one is the cost. The cost of MRI in the States is unusually high and it can vary between 2,000 to 3,000 dollars. In Europe, its much, much cheaper even with them privately and at most in the best facility that we have in the UK, its around 1,000 dollars for an MRI. Its a few hundred dollars in a NHS public facility because obviously that machine is working almost 24 hours. So, there is a cost issue and the insurers have to be prepared to allow the urologists to do the MRI beforehand. You know, NYU, Memorial Sloan Kettering, John Hopkins, UCLA, are all now doing MRI prior to biopsy. The academics at this have persuaded the insurance companies this is a good thing and I think many of the insurance companies are slowly learning about this and the other thing, I think, is professional competition gets in the way. This does require a urologist to work recklessly with the radiologist in harmony. You need, I need the radiologist's skill to tell me where the tumor is and the patient then needs me to use my skills to direct the needle into the tumor or _____ into the tumor, so we have really good working relationships with the radiologists, so we discuss cases together, we work together and that was so nice about this visiting surgeon from Florida who came with his own radiologist and they are both going to work together to improve the service they offer patients.

Mike Scott : Thank you. We can bring in our next panelist and Allen, you there?

Allen : Yeah. Yes, I am.

Mike Scott : Go on. Go on with introducing yourself and your question for Dr. Emberton.

Allen : Sure. I am in Los Angeles. I often act as a patient advocate. I belong to several prostate cancer support groups and love time online doing that. I was treated about three years ago using _____ and here its commonly called _____. What I would like to get back to actually is Mike's opening question about active surveillance. I have been looking at Dr. _____ study and he has 97% cause-specific survival on active surveillance and two-thirds of the men required no treatment at all and one-third did opt for radical treatment. I am wondering given the success, overwhelming success of that, is there still a niche for focal therapy and at the other end, owing to treat radical treatments like the one I had, _____ or HDR brachytherapy which has extremely low rates of side effects and extremely high cure rate. Does that sort of squeeze out focal therapy?

Dr. Emberton : Umm… So, focal therapy is not in competition to active surveillance. I didn't treat anybody with low-risk disease. We go to huge efforts to characterize men as low, medium, or high risk and we have published definitions of what we mean by that. So, focal therapy is in competition with whole gland therapy in order to reduce toxicity. All the treatments that you mentioned are being looked at, are first of all capable of focal treatment and are being looked at in trials as we speak in focal therapy and radiotherapy is particularly interesting for focal therapy and that can be in the form of seed brachytherapy, HDR brachytherapy, or indeed CyberKnife because if you plan focally, you can increase the dose to the tumor and increase efficacy and diminish the dose to the parts of the prostate or surrounding structures that you don't want to treat or indeed render the dose absent and so the opportunity in radiotherapy is slightly greater than in the ablative therapies because of this opportunity to dose escalate in the area that you want to. The reason that radiotherapy _____ increase the dose around the tumor is that they are limited by the dose they can apply to bowel and to bladder, etc., and that limits the upper limit. Once they reduce the target to a small area in the prostate, which they can now, because they have the necessary information, they can up, they can almost double the dose that they administer into that and at that same time diminish the dose into parts that matter. So, focal therapy is an opportunity to improve the efficacy of radiotherapy and also to diminish its harms and in the area of brachytherapy to reduce costs because you will be using less seeds. You pay for each seed. Most seeds aren't necessary. They are treating normal tissue and you can use fewer seeds and place them around the tumor with a greater dose and there are trials at Memorial Sloan Kettering, UK, and also in Paris, looking at that opportunity. So, its win-win-win, whichever way you look at it, but importantly the three treatments that you mentioned are capable of selective ablation.

Mike Scott : Allen, do you have a followup question?

Allen : Yes. Also, on the subject of multifocality, since about 80% of the time, prostate cancer seems to be multifocal and, as you said, with many of the foci below the limits of detection of even multiparametric MRI, I am wondering about identifying appropriate patients… I don't know if you saw it, but last week, there was a study published by _____ from John Hopkins and it was only an anecdotal study, a case report of one man where there was a lethal metastatic lesion and they traced its origin back to the prostate where they found that it had originated in a very low-grade cancer focus from the primary tumor. I don't know… It was just in one man, I don't know its true of lots of people, but if that kind of thing is generally true, will focal treatment ever really be curative?

Dr. Emberton : Well, that observation… I mean there's a _____, I haven't seen that paper, but the trouble with these papers is that that lesion, we don't know the direction of travel, so if somebody has got metastatic disease, that lesion could be metastasis. You don't know that it was the origin. All you know is that they share some genetic material. So, there's a kind of directional causality issue that is always raised and that goes against all our thinking about cancer. So, you know, all risk models of cancer relate to grade, that's why grade exists, low, medium, and high. Men with high-grade disease have a high probability of dying of the disease. Men with low-risk disease, as you just told me, with active surveillance have a low probability of

dying of disease. In fact, the latest thinking is that Gleason's 3 + 3 has never killed anybody in that its never metastasized to bone or to lymph nodes in many tens of thousands of men. So, whilst I take that observation, obviously I haven't read it, it goes counter to everything that we know, not just about prostate cancer but also against all prostate cancers and if that is true, if that single observation in one man is true and the observations that we have made in hundreds of thousands of men is incorrect, then we all have to pack our bags and go home. (Laughter). So, I think that it is interesting. I would love to know more about it, but I don't think its representative of most of the disease.

You know, I have a 50% chance of having prostate cancer today. I am 53, talking to you tonight. That's the rate at which I might have microscopic focal disease. You know, most of us, all of us will live longer or have prostate cancer and the background rate to lifetime risk of death is 3%. So, there's a huge discrepancy of prevalence and incidence. So, I am happy with uncertainty. You know, what we have done is try to find a threshold above which we will treat and that includes Gleason pattern 4 or Gleason 3 + 3 above a certain volume and 0.5 cc, that's almost certainly incorrect, but you have got to start somewhere and at the moment for the trials, we have limited. We created another threshold for disease beyond which we will treat because the risk of metastatic spread is so high that we wouldn't know if focal therapy made a difference or not and so at the moment, we have an upper limit of disease, a Gleason's 7, so dominant pattern 4, with no limit on multiplicity or indeed on volume and a PSA of 50 and I think that's reasonable and legitimate, you know, in phase 1 and phase 2 studies. The important take-home message, I think, is that we don't treat low-risk disease. We watch it. I think in the UK, we probably have more surveillance than anywhere else in the world and clearly we are not completely mad and not treating focally Gleason 8, 9, and 10, you know, so they are getting standard multimodality therapy as you would expect.

As we learn more and more about disease, as our targeted biopsies give us representative tissue so we can subject it to genomic _____ we will learn more about what constitutes a lethal lesion versus a non-lethal lesion. So, there is a lot to learn, but the opportunity for learning is in observing these small lesions which focal therapy gives us. If you hold the story with radical prostatectomy or radiotherapy, you will never learn. So, the only models in which we can learn about disease or active surveillance in focal therapy and therefore, that's not a complete but one justification for them and at the moment, I think, we are doing it within the bounds of safety and within trials which have obviously gone through patient panels and review boards or apex committees as we call them here. So, I think its a legitimate approach, but yes, uncertainties do remain.

Mike Scott : So, _____ bring in Rich Davis who is our last panelist. Rich is very involved as a patient advocate with the group at the University of California, San Francisco. Rich, you there?

Richard Davis : I am. Can you hear me?

Mike Scott : Yes, we can.

Richard Davis : Good. Good. Umm… Hello, Dr. Emberton. As Mike mentioned, I do a lot of work at the UCSF. I was diagnosed in 2007. I had high-risk disease. I selected IMRT plus brachy. So, I had about two years of hormone therapy largely because I wasn't a good candidate for the surgery. I figured I would need that anyway. Umm… And since then I do a bunch of advocacy. I sit with folks you probably know, _____ who was my doc…[00:50:22] …and Chuck Brian and others on the efficacy board there in the research. My question is about the role of focal therapy for salvage treatment, where a patient has already had sufficient radiotherapy. I am wondering whether… I am wondering what the role is for cryo and for HIFU. I have seen more recently that we are starting to use cryo salvage therapy…and I would just like to hear your thoughts and your comments on that.

Dr. Emberton : Yeah and great question! So, one of the fascinating things about radio recurrent disease is that its more likely to be unifocal than multifocal. So, recurrence tends to be focal and that's fantastic for us in terms of treating because it means we can limit the energy to a small proportion of the prostate, whether it be through heat or cold and therefore limit toxicity. The trouble with treating at the whole gland level, you

know, surgery for instance, and after a high dose of radiotherapy and you had the absolute limited dose with IMRT and HDR, that's the mechanism by which you can get most dose into the prostate is that if you do anything to the prostate, because of the blood supply, healing is compromised and the side effects like incontinence and rectal injury are very high. So, we published a couple…

Richard Davis : Uhhh… We know.

Dr. Emberton : Yeah. So… And, you know, they are devastating. You will know patients who had either or both of those or sometimes worse, complete stricturing of the prostate afterwards and left with suprapubic catheters that block and get infected, etc., etc., and end up with an ileostomy. Its an awful, awful situation. So, again, its imaging, its MRI, CT, chole, PET that allow us to localize the disease and then target our therapy to the disease and preserve tissue and if another lesion appears two or three years later, we can treat that in the way that we treat bladder cancer and that has diminished the toxicity significantly and we recently published our first series doing focal therapy using HIFU, but we are using cryo as well, and we will be using other any sources in the future to do this.

In terms of oncological efficacy, the freedom from disease rates look very, very similar to whole gland treatment, as you would expect and this population obviously has a high proportion, these men have microscopic metastases _____ recur distally, not locally. So, I think the opportunity for men who do recur after radiotherapy and some of these recurrences can occur quite late. If picked up early, in other words when the PSA starts to rise, we can identify these foci very, very clearly by MRI and the bit of the MRI that's critical is the gadolinium component because the background signal of the prostate, because of the way that radiotherapy works, the blood supply is reduced. There is an endarteritis. In other words, radiotherapy works on the small blood vessels and therefore the background signal is very _____. There is very little noise and the cancers light up like light bulbs. They are very, very clearly seen and very visible and _____ be very small and maybe amenable just to one-needle treatments, which can be done, you know, in 10 minutes as a daycare's procedure.

Mike Scott : So, at this point we have about 7 or 8 minutes left and I know we have probably got some patients on line with questions. So, Priya, I am going to hand it back to you to see if we can get a couple of questions from our listeners?

Priya Menon : Thank you, Mike. We have actually lot of people lined up to ask their questions live on air. Professor Emberton, I will be bringing them one by one. We have around 8 to 9 minutes, maybe quickly, briefly, we can……try to get all of them in. Yeah. The person calling in from 515-276, please ask your question.

Caller : Yeah, that's me. Two quick questions. One, who is the Dr. _____ you are talking about?

Dr. Emberton : (Laughter) I don't know. He hasn't given me permission to broadcast his name. But he works out of Jacksonville.

Caller : Okay. Second question… Second question. A lot of the places like here in the US are doing MRI prior to biopsy. They are doing what's called the cognitive MRI. That's familiar to you, that term?

Dr. Emberton : Fine. So, the cognitive bit refers not to the MRI but to the way in which the targeted biopsy is done. In the only study that's compared cognitive versus computer registered, cognitive won and if you look at one study that was published under my name, recently published in _____, I think we have the… I ____ this is cognitive, me looking at the MRI and then finding the needle. I think that's the study with the highest detection rate currently in the literature. So, cognitive in good hands works very well, but you have to be very skilled. I think the learning curve is quite long. What registration does is allow somebody who has not been used to doing this, we have been doing it for years and years and years, to get up to speed, to kind of super pro level, you know, overnight because the target has presented on the ultrasound. Its not a difficult procedure to do.

Caller : Uhmm… So, one followup… So, when you do a cognitive biopsy, can you use the ultrasound to kind of see where that funny thing on the MRI actually is or is it visible on the ultrasound?

Dr. Emberton : Yeah. Ultrasound itself doesn't usually detect the abnormality. What MRI tells you to do is where to deploy the needles. So, if you are doing cognitive biopsies, you tend to have to use a few needles to overcome the error. What the registration does is take the information from the MRI, transfer it on to the ultrasound, so when you look at the ultrasound you see this little halo or area that looks pink or whatever color they choose to make it and you can stick your needle right into it. So, your accuracy goes up and therefore the number of needles that you require will go down and you are more likely to get a direct hit and therefore, representative tissue which allows you to then risk stratify accurately.

Caller : Right. Thank you so much.

Dr. Emberton : Pleasure. Thank you. Quick question.

Priya Menon : Person calling in from (718) 767-2262, please ask your question.

Caller : Yeah. Here, in the US, using NanoKnife for prostate cancer is very, very new but no long-term data. Is there any long-term data on its use for prostate cancer in the UK or elsewhere?

Dr. Emberton : No. I have done more, I think, than anybody else currently. I think I have done 26 cases. We have just teamed up with Sidney to pool our data and that paper is just being submitted, but there is no long-term data. The longest followup we have is 18 months. You know, its a very nice technology. Its a very quick technology. I think its a very good tissue destructive technology. It can create very nice, small, neat lesions and preserve architecture, so I am very, very excited by it and its non-thermal, but there is no long-term data.

Caller : So, Dr. Emberton, I have a quick question for you. I am the next person on line. How many different forms of focal therapy are you actually using at the moment?

Dr. Emberton : So, I... I diminished the importance of the energy source. I think the types of focal therapy you can relate to your definition, your ceiling and floor definitions of disease. So, the first trial we did was anatomically defined, so is hemi-ablation study. You know, as we treat the left lobe or the right lobe_____ not doing a left or right mastectomy. The second study was published _____ oncology was any cancer that we detected was treated, which is a completely different approach and the third one, which has not been published yet but just about to be submitted, is an index lesion approach where we treat disease above a certain threshold and knowingly leave disease below its threshold and that's kind of what I call an index lesion approach and that study is just about to be submitted. There's another study now with long deserved outcome using that approach, which I think is the way forward and so I see the big difference is in focal therapy as the kind of approach to the disease. I think the energy just needs to be tailored to the individual. If the lesion is very anterior, I can't reach it with HIFU because I have a 4-cm focal length, but I can reach it with NanoKnife and I can reach it with cryo. If the lesion is very posterior, then HIFU is an excellent source of a treatment, so I think the focal therapists in the future will have to use a number of energy sources, including radiation sources as a potential low focal therapy and in the future possibly injections and we may be able to turn focal therapy into an outpatient procedure where through image registration we just inject a toxic substance into the cancer, remember these lesions are fairly small, under local anesthetic. So, it will be a bit like going to the dentist and that's the way I see it playing out in the future.

Mike Scott : Thank you. And so, Priya, perhaps you can bring our next question on line.

Priya Menon : Yes, Mike. The person calling in from 585-244, please ask your question.

Caller : Well. I have two quick questions. First, it was my understanding that here in the US the FDA has not yet approved HIFU. I thought I was going to have to go to Toronto, Canada, to get it, but I heard someone earlier mentioning a doctor in Boston, I think the name was Pianti or Kianzi, something like that… and then

you mentioned to everybody in Florida, so can it be gotten here in the US and the other question is can you elaborate on the advantages and the disadvantages in terms of success rate and side effects and so on between the different focal therapies like cryoablation and HIFU and _____.

Dr. Emberton : This is not a quick answer. So, first of all, you cannot have HIFU in the US FDA jurisdiction. You have to go out of board. So, you have to go to Canada and I think Dr. Scionti works out of Bermuda or some other places. I work with Dr. Scionti. He is an excellent HIFU and cryotherapist ____ increasingly doing more and more focals. So, he is…, you know, I can vouch for him. I have worked with him. I have seen him operate. I have heard him lecture. We are good friends, but you will have to have your treatment outside FDA jurisdiction. In Canada, there are also some very good focal therapists in Toronto. So, I think those two sources would be good, but otherwise you can't have it done. I don't think there is much difference between the therapies. I think there's difference, slight differences in toxicity between the approaches. If we treat less than half the gland, you can pretty much guarantee preservation of erections. Got more publications coming out on that. The less you treat, the more you can keep ejaculate. I think incontinence now is a thing of the past in focal treatment. I actually don't bother telling patients about being incontinent because the incontinence is so incredibly rare and we spend our time discussing the quality of the ejaculate rather than potency or continence, you know, when we meet postoperatively.

Caller : So, will somebody still be fertile if it is focally treated?

Dr. Emberton : Well, I think… I think, you know, fertility is… So, if somebody tells me they care about fertility, I ask them to preserve semen and also to try and conceive naturally because as we know, you know, fertility is all about maximizing probability and, you know, but so its not a… I can't offer any guarantees in that respect and I would be very, very cautious if somebody still wanted to have family, but you know, the usual things would apply, save semen, you know try and defer for the intervention and, you know, spend this three to six months trying to conceive naturally.

Caller : Okay. Thank you.

Mike Scott : Priya, I think we spoke to _____

Priya Menon : Ah, yes. Yes, Mike. Just one last question. This is a… What is the cost for a US national to receive HIFU therapy in London?

Dr. Emberton : Sorry. Hello. What's the cost, what?

Priya Menon : Yes. What is the cost for a US national to receive HIFU therapy in London?

Dr. Emberton : It would be around 11,000 pounds, so about 13,000 to 14,000… You will have to do the conversion rate yourselves. So, that's cost of the…, complete cost of hospital stay, equipment, surgeon, and anesthetic.

Priya Menon : Oh! Thank you. Thank you very much. I think…

Dr. Emberton : 11,000 pounds.

Priya Menon : About past our time and, Professor Emberton, I think it has been a absolute pleasure to have you with us today. Mike, Jim, Rich, thank you for a very informative discussion and we thank all our listeners for their support and the link for today's discussion will be sent via email to all participants. We hope to meet all of you for our next Cure Panel Talk Show, which is the 7th of November. We are talking about yoga for healing. Please visit trialx.com/curetalk for all details on our upcoming shows. Thank you. Thank you very much.

Mike Scott : Thank you. Thank you, Mr. Emberton. It was a pleasure.

Dr. Emberton : A great pleasure. Bye, bye.