Developing Studies for Prostate Ablation
Related Energy Devices
(SPARED)
CRN Think Tank Meeting
July 10, 2018

Transcript

Jim Hu: Greetings everyone, I'd like to adhere to the timeline and have a lots of time for discussion and so well, why don't we start off quickly with my slides, please. It's interesting as I am coming over in the shuttle with Jim Wysock and actually got a car ride from Mike Gorin when we are talking about these studies and so it is a great to see that everyone is up to date on this.

Some of this is overlapped little bit with the ODAC meeting tomorrow and we will talk a little bit about that because many of you may be staying for that, and Dr. Carol was kind enough to come earlier. The main things that I will talk about today is related to again, in the spirit of what we are talking about – cancer control outcomes to review some of the more recent literature but if you come through this quickly because I know there is lot of, again expertise and individual thoughts about study design and outcomes. So, see do I have control here? Ok, so.

So, again. There may be a certain overlap with tomorrow which is certainly fine and I will be speaking to a little bit different audience, but again I think that we all know that the push towards partial gland ablation is somewhat driven by patient preferences and so in terms of some of the important things that the patients that we heard about in the past are presentation of ejaculate volume. I think certainly these patients when they come, they know that they are somewhat compromising on cancer control. Next slide, please. This just sets up some of the updates in terms of very recent studies that have come out, looking at the different ways of conducting focal therapy. Next slide.

And so, actually, I got an email from Dr. Scardino, I think it was two days ago, mentioning that this is now in press, this is the update to the TOOKAD study showing continued lower probability of conversion to radical therapy after the end of the two year study. Next slide.
And again, looking at in-field progression, the TOOKAD arm to continues to have less in-field progression. As a reminder for those in the room who are not as familiar with this, this is the only level 1 evidence as far as I am aware of focal therapy in comparison. In this case it was to active surveillance for lower risk - for Gleason 6

prostate cancer so the hemiablation with the VTP or with the TOOKAD apparatus and again showing subsequently for biopsy there has been less in-field progression.

And for just a segway for tomorrow some of these discussions are related to patient selection it should be, we will be treating lower risk cancer patients. I think this group and I believe this is a meeting of FDA, now that I think we are little focused differently in our discussions about cancer control indications and I hope, I think, we will talk about that more as the afternoon progresses.
Next slide, please.

So, this was just in preparation for this meeting – finding also not just urologists alone are interested in partial gland ablation, but this just shows a trial on the partial gland ablation with brachytherapy and again we will see some endpoints here that may be able to refer to as Art talks about OPC coming up with the cancer control outcomes - what it is about and what it may be. Next slide.

And so looking at metastasis as an endpoint, we can see that even when brachytherapy for partial gland ablation is rendered, and this was under MRI guidance, that the likelihood of the metastatic disease at 10 years for intermediate risk is still going to be relatively low. And we will next we look at an active surveillance series. So, when we talk about partial gland ablation with cryotherapy we find -- Next slide.

This was actually I think it was slide has got little out of order that but this was actually a single series center comparison of a HIFU vs robotic assisted radical prostatectomy. So, this came out in the Journal of Urology earlier this year. Next slide.

And I think this shows that the focus on preserving quality of life is intact there on the left side you see the preservation of continence and on the right side the IIEF scores with the radical prostatectomy of course in the left column in part B and in the green bar in terms of recovery of continence and so, at least in this French center, they did pretty well in terms of preserving quality of life – Next slide.

And then, not unexpectedly, when one looks at additional treatments for the partial gland ablation – there was definitely a higher probability of a needing additional treatment as compared to the radical prostatectomy group. Next slide.

And so, this looking at any ends - kind of bringing all this together so that it can further our discussion this afternoon. This was just a consensus panel and I think there are some members of the audience for today that were certainly on this and can reflect on

their experience and perhaps further be drawn upon - with the treatment rate of 20% with focal therapy; that's clinically acceptable. Next slide.

And then more recently, in just the last couple of days, this came out in press and this was basically a registry in the UK of some of these devices where in the UK that is mandated, there was a collection of data for partial gland ablation. And next slide, please.

And so, similarly to the single center French study, we can see that continence rates are fairly in line with what we would expect in the terms of the partial gland ablation – ranging from really a 100-97% when you are talking about 0 pads or 0-1 , 80% with no leakage at all. Next slide.

And then here, I think, just setting up again, foreshadowing when we are talking about the treatment selection group we can see here that of course for the high risk cancers that were included there were much higher failure rates and when we think back to the at least the metastasis free survival from the brachytherapy cohort as a frame of comparison trying to understand difference in the population that may inherently be there.

Next slide. I think one critical thing to note when you think about pragmatic, clinical registry network for registry data versus randomized trial as part of the design getting a biopsy at the end and how we saw that at least in this study is the relatively small number of these men that underwent biopsy subsequent to the study. And so, again if you look at the treatment free survival it's a softer endpoint but it is interesting that when you look at the 220 men, roughly 40% that had a biopsy almost half of those - 111 - had a biopsy because it was part of the study design because a lot of these men were culled from a trial that there was already phase 1,2 and 3 trials that were being conducted so, 111 in other words or 20% of the cohort had biopsies that were off-protocol at the time.

When you look at the participants that had a biopsy, you can see that the in-field recurrence was 18% the out-field recurrence was 12% but there was very little in terms of the description of what indications for biopsy were or the technique. Next slide.

From the UK as well there was another registry that this was the abstract from the AUA last year. Next slide.

It just shows that the study design, at least for the prospective recruitment and randomization for intermediate risk disease comparing radical prostatectomy to high intensity focused ultrasound. And the goal of this abstract was just to say that at least in

these investigators' minds it was possible to enroll such a study. So, again I just want to - very briefly and I stayed under 10 minutes - give overview of some of the, I think more recent data that, some of which came out in the last week just as something of the jumping off point for more conversation. I will turn it over to Charlie here.

Charles Viviano: Thanks, Jim. You know, I realize in our eagerness to be on time in starting this brief meeting that we didn't really go around and do any introductions. There are many familiar faces here but a few new, so maybe it will be a great idea to just to whip through and do some really brief introductions. Just name and affiliation, John, you want to start upfront?

[inaudible]

So, first of all, let me take this opportunity to thank you and welcome you to the FDA this, morning – this afternoon. We appreciate that you have been able to make time for this meeting prior to the ODAC meeting tomorrow.

Because we have, we really need your input. I thought I'd just take a minute or so to discuss sort of where we have been in the center for devices with regards to the high intensity focus ultrasound or HIFU devices to try to help us understand where we are currently and where we'd like to go forward.

So, many of you are probably aware of that 4 years ago the two sponsors, the manufacturers of two HIFU devices came to the FDA center for the devices with PMAs or pre-market applications for class 3 devices. They indicated at the time for the treatment of localized prostate cancer.

The first kind of these devices, the first current indication, they actually went to advisory panel - some of you were on those panels - and the end of it all was that they felt that there were no clinical relevant endpoints associated with the indications for the treatment of clinically localized prostate cancer.

Subsequently the sponsors actually wound up withdrawing those two PMAs. With further collaboration between the FDA and those sponsors, eventually a path forward was settled on to pursue a tool claim. A prostate ablation tool claim for both devices – specifically there was no indication to treat any prostate-specific disease that's actually written in the specific regulation that we wrote for these two claims, these tool devices.

And in November, October/November of 2015 the two devices came to market through the novel pathway, a class two pathway as prostate ablation tool devices.

Initially, we had our first meeting shortly thereafter, I think in July of 2016 was the first meeting here. And I got to be honest with you – Ben Fisher, the division director and I we said: I know that they are going to want to have a prostate cancer indication. They wanted it upfront, they didn't get it upfront and I know that they are going to want it. I know that they want a cancer indication, everybody does.

The concept behind the SPARED or the Studies on Prostate Ablation Related Energy Devices is CRN - coordinator registry network - was really born out of a multi-group effort to identify… Collecting the information that might be needed for a prostate cancer indication, post-market.

To our dismay, some might say… Amazement is probably a better word, the two sponsors absolutely said that they did not want a prostate cancer indication in 2016.

They were ecstatic with the prostate tool claim, essentially everything is on-label as a tool from their perspective and they didn't indicate at all that they wanted to pursue to a prostate cancer therapeutic claim.

And so, we have moved forward with the SPARED effort. Over time, however, things have kind of circled back. And we are now getting information from some of the manufacturers that they are actually very interested in getting a prostate cancer treatment claim.
And it is tied pretty much to reimbursement.

I am not with the CMS, we don't have CMS here today, we had CMS at some of our prior SPARED meetings, they tend to be a little tight-lipped about what they have to say at these meetings; they don't want to commit without thoroughly investigating it, but sounds as reimbursement can move forward – the rails would be greased if there was a prostate cancer indication claim from the FDA or these ablation tool devices.

And so, there has been renewed interest within the past 6-12 months or so from external FDA forces to pursue a prostate cancer indication treatment claim.

So, where we are as a center right now, is trying to identify the information that we think we need to support such a claim. And that is tied in with the SPARED as to what information the SPARED effort would need to collect to support that effort.

And which brings us here today. I thank Jim and his colleagues, it was on a phone call where he said: "Hey, we have all of these brain power around prostate cancer coming in

on July 11th. Do you think we can get folks to come in on July 10 and sort of kind of help leverage some of that. Folks are going to be in town to talk about these end points and the study design."
So, from our perspective, purely here is to listen to what people think and what people think will be important in moving forward with the prostate cancer indication. Now, the reason back in 2014 that the advisory panels, I think, didn't see the clinical benefit risk balance favorably at that time, no one was willing, no one had the data on typical cancer outcome that were so familiar with 5 years disease free survival , 5-year overall survival, metastasis free outcome etc.

And for various reasons, I know we have some of our cedar colleagues today, you know, it is for devices we typically don't get 5 or 10 year studies with 2-5000 subjects on them. And these are various reasons for that. The sponsors are a little bit different. We don't have very very many Pfizers and Astrazenecas etc.

So, the ability for us to do that sort of study is limited. So we are left with trying to identify other endpoints that are perhaps more feasible for devices makers due to need and to investigate for that therapeutic claim.

So, just a few thoughts before I turn it over: Some of the things we are interested in hearing are what should those studies look like, what is the reasonable end point that would support a therapeutic cancer claim for these ablation devices. Who would the comparative group be? And would that vary based upon the inclusion population? Does it vary if it is intermediate risk or high risk populations?

At this point I think there are some high-level questions that the agency is interested in hearing about and proposals, hopefully, that will come from this that will help us focus our efforts with the manufacturers to potentially move forward.

So, again, thank you for being here today
And at this point I want to turn it over to Mike Gorin from John Hopkins who is going to talk about focal therapy for prostatic cancer: lessons from breast cancer.

Michael Gorin: Got you.

[Question from audience, inaudible]

Charles Viviano: Yes, but maybe I should tell you what we got for the ablation claim. That would kind of help focus moving forward might be what we need for our cancer claim.

We got the ablation claim that was 12 or 24-months posttreatment biopsy data. PSA nadir data and prostate volume data. That is what we got. We got it on about 100 subjects – This was, there were two studies - one was naïve therapy, whole gland. The other was salvage therapy, whole gland after initial therapy failure. That is what we got. The panel told us that probably wouldn't cut it for a cancer indication. As for what would work - we don't exactly know yet.

I think a little bit depends upon what the thought leaders say would be a reasonable endpoint to support a cancer indication and in these discussions at the AUA, on line, and on the phone,
I've heard a whole lot of suggestions – time to retreatment, combinations of imaging and markers, and biopsies and various.. and restaging people back to active surveillance etc etc.

So, I think what would be required from the FDA would be based upon what the thought leaders would think would support such a claim. I know that sort of a wishy to washy answer, but at this point we don't know exactly what you think would be necessary to support a prostate cancer claim for devices like this.

[Question from audience, inaudible]

First of all, we have a guidance that says that we accept OUS data there are some parameters that have to be met, there has to be some pool-ability amongst populations, we're pretty clear on that. From that perspective it doesn't have to necessarily be US data so that wasn't the issue.

I can tell you I am looking at John Baxley on the end. How to phrase this? We cleared that—so, that went out, so that is public. But, there was one of the sponsors that came in to expand the labeling for one of their iterations of their devices in US. They told us that they gave us this cobbling of a couple of studies together to meet our soft minimum of 100 subjects.

But at the same time they told us, you know, that these devices have been used with 10's of thousands of subjects around the world. The best we got was this hodgepodge of small studies to come together for their application. I think part of it has to do with… There were differences in what we might have required moving forward. Biopsies for cause, for example. A lot of these folks had biopsies for cause. We are interested in scheduled biopsies in the studies. So actually trying to find data of X-thousands of subjects of who they've done. We didn't think we set a very high bar, to be honest with

you, but apparently there was a lot of difficulty in meeting the bar that we did set especially when it came to a scheduled biopsies, not biopsies for cause.

[Question from audience, inaudible]

It was difficult for us to review that and I can tell you it went through many iterations. The first attempt it didn't make it through even that low bar – we in all fairness – we were not thrilled with it either. But, eventually we were satisfied with the evidence that we were presented. But we were surprised it took as much effort to present what they did present to us.

Ben Fisher: So, I think you have to also consider where we were, so Art, I really appreciate your comment there. Right, 100 patients. You know we had two panels that shut down the indications that had come in for cancer and basically the situation that we were facing was that this technology probably has utility, how can you get it out there to the position of evaluating it. So, we struggled about that, was it going to be a cancer claim, no it wasn't going to be a cancer claim. So, we chose to try to find a tool claim and it was very bland. It was for prostate tissue ablation and to tell you the truth, they didn't even have to hit a tumor.

The only thing they really had to do, I'm serious, the thing that they had to do was – we said you need to show us, you need to define the region that you want to hit and that you are going to fry or freeze or whatever you are going to do to it. You got to show us that you can contain it within that space and that there was no collateral damage to any of the surrounding tissue or any of the other structures that are in there.

We would have loved to have treat and resect data and moving forward maybe I would say that's something we'd need to put on the table, right? But, what we did was, we held it to that low bar – saying just ablation of prostate tissue. Now, I will say that when we granted the de-novo and the 510-K was granted a week later, we were faced with press releases all over the place, "HIFU approved for cancer treatment!"

And we had to go back. NO,NO,NO! So, you know, no good deed should go unpunished – we tried to do what we could do to get the technology out there. We are hoping that through either registries or through a clinical trials that we would be able to get- like I said, or like Charlie said also. We thought that the next step was going to be a progression towards a cancer claim only to have the sponsors to say no, we're happy where we are. But, you know those winds have changed also.

Jim Hu: I just want to say one more thing, that I think it also illustrates and reflects that the study that just came out from the UK. That is the registry, folks that are authors on that paper are also part of these societies, part of the trials where there was inter-trial biopsy – but yet we can see that one of the challenges with the registry is going to be that only 11% of people are getting a for-cause biopsies with a median follow up of 5 years.

So I think that just kind of highlights the differences when you are trying to point out their study design vs if we are going to look at the registries – how people may stick to those practice patterns.

Charles Viviano: And just one last comment. Just something to think about is what the FDA gets or requires for their studies may be different then what is commonly done in practice.
Especially if it is not academic practice just private practice etc.

Probably, if you go to the private practice where there is not an interest in the registry or collecting the data per se - you may or may not have anything but for-cause biopsies – that is a possibility and for this group moving forward - just a thought – we may – the agency may require the center might require more rigorous data, although you are amazed how little we've taken but

[Comment from audience, inaudible]

So one last, last comment before we move on is that I appreciate what you are saying. We heard a comment back down here about a benefit/risk so we were having these conversations from a regulatory point of view, that benefit/risk may change depending on the patient population and how it is used

So, one of the things we need to take into consideration and discuss today – people coming in for an indication, are we talking low risk patients? Are we talking high-risk patients. Are we talking first line treatment or salvage therapy? For failed therapy prior to that? So, these are all the things we need to take into consideration and actually help us or well, sometimes muddy the waters with that risk/benefit.

Michael Gorin: So, good afternoon, I am Michael Gorin, I'm one of the new junior faculty at Johns Hopkins. I would like to talk to Charlie, Art, and Dr. Hu for putting together these meetings. My first one was two years ago, when actually I was still a chief resident and I've really been inspired by the conversations that I've had here and have gotten really quite involved with the SPARED registry. The context for that talk is

that over that two year period as Charlie has said – we had spent a lot of time designing and being in the early stages of deploying a registry and it became obvious – I think the paper that was published in European this week is a good example of it – that registry data, while helpful, only takes us so far and the real world data is just insufficient for getting a cancer claim established.

And so, in our many conversations we had said – well I think – well, we think someone's going to need to bite the bullet eventually and perform a randomized clinical trial or some form of clinical trial to prove efficacy for prostate cancer. So, that was the context for today's meeting so I wanted to give a talk on what has been done in breast cancer as they have been able to successfully carry out these randomized trials.

And Dr. Eggener has given talks on this before, he's written on this before, so I am really thankful for him providing me with some slides today. So Dr. Eggener please chime in at any point if you wish to add.

So, I will start by sharing an email that Dr. Eggener sent prior to today's talk. I wasn't sure if he sent it to me or to everyone on the thread, but I thought it was kind of cool and he said my stellar rep is sliding by participating in the focal therapy crowd. Next slide.

You know, I'll just say that I don't --I think like many people in the room here today, you know I haven't fully bought in to the focal therapy but I am certainly hoping that we can come together and develop a trial that would allow us to demonstrate its efficacy. Next slide.

I really think it could be fantastic for our patients, someone had said earlier with the improved toxicity profile, if we could perform focal therapy , but also more of it is, as a young guy coming into the field – I don't want also to end up like these dinosaurs here and so that is a reason and part of my energy for focal therapy as well. So, next slide will actually begin the talk now.

So, again this slide has been covered - basically the content of today's meeting – the fact that SPARED has been around for 4 meetings now, next slide. Just to highlight some of the successes to date. Out of our first meeting we have published a DELPHI method paper where we came together as a group and really nailed down what variables are thought it would be necessary to include to make a quality registry.

We currently have two standing committee as part of SPARED, the IT and the partnership committee , myself and Jim Wysock head out the IT committee , Dr. Bianco and Dr. Hu head out the partnership committee and we have been having near-weekly

phone calls for probably 8 months now or so – so it is really pretty exciting how into it everyone has become.

We have successfully built out a red cap registry and we are in the process of getting the data use agreements up into the early stages where we can actually start recording data and sharing it and really what is nice about these calls - a meeting like today came out of it and we said that we need to think beyond. Next slide again.

This audience does not really require that slide but suffice it to say that the treatment of prostate cancer saves lives. And these are data from the SPCG-4 which essential showed that radical therapy as radical prostatectomy decreases the risk of death from prostate cancer and it improves overall survival. The next slide.

This comes at significant cost in terms of side effects and again these data are not foreign to this group but from Dr. Sanders paper we know that a significant number of men suffer from both urinary side effects, as well as sexual side effects – whether its prostatectomy, radiotherapy or brachytherapy. Next slide.

So, it's all about managing the toxicity and the efficacy of that therapy and the thought is that if we can make the therapy less radical – then perhaps we can improve that toxicity profile.
But, of course by making them less radical, we worry about the efficacy and these ideas are not foreign concepts. Next slide.

So, it is important to acknowledge that there are a number of widely accepted forms of focal therapy both in our field and throughout the field of oncology. And the concept of focal therapy for a malignancy is really not so foreign.

Of course, we have partial nephrectomy for renal cell carcinoma supported both by large series clinical data as well as by randomized controlled clinical trial. Transurethral resection of bladder tumor is something we perform everyday as urologists as a treatment for non-muscle invasive bladder cancer. Wedge resections of lung and liver and also subtotal mastectomy a.k.a. lumpectopy for breast cancer. Next slide.

So, among of all of those examples, the one that urologists seem to time and time again have latched onto to analogize focal therapy for prostate cancer to is lumpectomy. It's been called the male lumpectomy in a number of different papers, prominently displayed in the titles, abstracts etc.

So, I really wanted to make this talk about, you know, if we're going to analogize focal therapy for prostate cancer to breast cancer - what did it entail to actually make lumpectomy a thing for breast cancer? Next slide.

So, just to tell the history of lumpectomy. So, in 1894 William Halsted at John Hopkins hospital developed, alongside some other surgeons, what is known as the Halstead radical mastectomy a truly radical surgery for localized breast cancer. This surgery involves removing of the entire breast, the nipple, the pectoralis minor muscle, pectoralis major muscle- all the way down to the chest wall. This left women with absolutely horrific scars as you could see on the right side of the screen there.

A truly radical surgery with very, very significant quality of life [inaudible]
Around the 1960s people have looked at this procedure and said: ''This is just simply far too radical, there is a horrible quality of life implication here, can we modify in such a manner that we can make the scars from this surgery, better for women. And, so the modified radical mastectomy came about.

It was first shown in case series, but then in 1977 a randomized clinical trial was actually performed comparing modified radical mastectomy to the Halstead radical mastectomy.
This paper was published originally in Cancer and then subsequently in the New England Journal, Bernard Fisher was the first author on the study and it showed there was an equivalency between these two and beyond a shadow of a doubt at this point , the modified radical mastectomy became the standard of care for sparring those women the quality of life imposition. Next slide.

Looking to and then take it to an even more minimally invasive approach, the concept of breast conserving therapy - a breast conserving therapy with lumpectomy was developed.

Randomized clinical trials were performed, comparing modified radical mastectomy to lumpectomy – either with or without radiation therapy. And in the landmark 1985 clinical trial, again published by Fisher , he showed that there was equivalency between these two techniques for treating breast cancer. Next slide.

So, here is actually the data from the original 1985 paper. Now it is important to realize that this trial had to be conducted starting around the 1970s. The first clinical trial to ever be performed in the late 40s up to the early 50s – so this study formed on the heels of the very very early experience and very early knowledge of the science behind

randomized trials which is actually amazing. I think the most interesting part is how they drew those charts by hand.

But anyway, so you can see here what the early experience of the 5 year data looked like here comparing women who underwent total mastectomy versus the segmental mastectomy – now which we call lumpectomy. Next slide. These data have subsequently been published a number of times, most recently in 2002. Now with 20 years follow up.

Unbelievable, 20 years follow up to show complete equivalency between these techniques. Next slide. Again it was that 1985 RCT that really showed that lumpectomy was safe, however, next slide. But really 12 other trials in that amount of time, have shown the exact same thing. Imagine that, 12 other trials whereas in urology for focal prostate cancer therapy we only have [unintelligible]. Next slide.

So, in the annals of oncology, the ESMO trial – there has been meta-analysis performed on this, depending on some other trials that additional biases if you include them in here – you could say 18 trials that have compared lumpectomy to radical mastectomy, you can see there is completely equivalent overall survival on local/regional control with lumpectomy plus radiation versus mastectomy.

And it is because of these high quality level 1 evidence that lumpectomy is a household word. It forms the backbone of minimally invasive breast cancer treatment and is the number one choice for women who present with stage 1 and two breast cancer or perhaps some of those who present with T3 breast cancer but have limited tumor size. And so, as I've already stated, the history of focal therapy for breast cancer has directly mirrored that of prostate cancer.

And I would like to take you through the timeline of the two of those and again, these are the slides that Dr. Eggener provided. So, in 1894 Halsted developed the radical mastectomy and in the 1940s Millin developed the radical prostatectomy.
So, we are about 50 years offset from the experience of breast cancer from the get go here. Next slide.

In the 1930-40s lumpectomy was first developed you know- very early case reports, small case series – right around 1995 focal cryotherapy came on the scene.
Both of these were met with skepticism, doubt, and ridicule.
Next slide.

In the 1960-70s case series and case control studies for the treatment of breast cancer came to be and that is really where we are right now with focal therapy. You know, we said that one of the best studies to be published was in European Urology this week and clearly there is already lots of scrutiny of it because it is nothing more than a case series, right?
Next slide.

The first RCT was reported in 1985 but started in the ‘70s. In 2017, we had our first reported RCT for focal therapy for prostate cancer. Again, somewhere on the order of 30-40 years behind where we’re at with breast cancer. Next slide.

So, based on all that work those 12-19 randomized trials - depending on how you count them – the rates of lumpectomy have risen from 10% to now 80%. In 2060 when we finally catch up to where breast cancer is at – it is questionable where we will be. Next slide.

So, it is important to acknowledge a very special individual when we talk about the topic of how breast-conserving therapy came to be and that is Bernard Fisher. Bernard Fisher was a surgeon at the University of Pittsburgh and he was really special individual. In 1956 just about 8-9 years after finishing medical school he was selected to lead the national surgical adjuvant breast and bowel project.

In 1958 as head of the NSABP he led a clinical trial, the first randomized clinical trial that the breast community ever seen to examine adjuvant thiotepa.
And this trial was developed on the heels of the first randomized clinical trial ever reported looking at streptomycin for TB in 1948 so within 10 years of that groundbreaking work, the breast community was very involved in randomized clinical trials.

Many of the trials that he ran through the NSABP fundamentally changed how breast cancer was treated - led to the modified radical mastectomy, lumpectomy, adjuvant chemotherapy, chemoprevention with aromatase inhibitors etc. For this was amazing work, he won the Albert Lasker clinical research prize, served on the board of directors of the ACR and as the president of ASCO. Next slide.

Just some quotes from Dr. Fisher because I think they will really resonate this group as we think about planning a clinical trial.

“Surgeons had been trained to do radical surgeries like all of us were – they felt that performing the lumpectomy was totally inappropriate . My peers were my antagonists.”

Next slide. “It was difficult to get doctors to put doctors into the trials and as might have been anticipated, it was even more difficult to persuade women to be randomized to a study in which some of them would undergo mastectomy and others would have their breast preserved.”
And I can tell you as the trainee of Dr. Walsh, he believes that this is going to be one of the problems that we are going to have randomizing men to radical prostatectomy. Next slide.

So, who will be our Dr. Fisher?
Well, I think we already have one.

[Shows picture of Dr. Jim Hu]

Hahaha.

[inaudible]

So, you know in many ways, I think Dr. Hu and Dr. Viviano and Art are all sort of serving in some ways as our own Dr. Fisher. Sort of rallying the troops now for the 4th time at the FDA to get us to put our minds together, this time towards a randomized clinical trial. Next slide.

So, but do we have the stamina for randomized clinical trial in this? I think it is clear that we do not. And that is if the endpoint is going to be overall survival. Because of the slow natural history of prostate cancer, we will start a trial like they did in the 70s and look at it in 1985 and you know technology will have moved on. I don’t think we have the stamina for it. Next slide.

But thankfully, there are earlier surrogate endpoints that perhaps we could use, and I bring this up so the group could discuss these endpoints more at large. That potentially, we could design these trials towards, that will make it possible for us to actually have the stamina. So, just recently, I think this made pretty big news - the ICECaP working group put together data from many different adjuvant prostate cancer trials and looked to see which earlier oncologic endpoint correlated with overall survival so that endpoint could potentially be used instead for drug trials. And what they showed is that metastasis-free survival correlated phenomenally with a correlation coefficient 0.91 with overall survival. Next slide.

And as a result of these data and data like them, that now for the first time, the FDA, on the drug side has approved a drug, in this case apalutamide, for the treatment of non-

metastatic castrate-resistant prostate cancer. Essentially, cutting the trial time in half – so, needing metastasis-free survival rather than overall survival as an endpoint to get a drug approved.

Now, I am not saying that's an endpoint we should use for a focal therapy trial, but I do think that there is hope and there is promise as we look at these intermediate endpoints. Next slide.

So, just in conclusion, focal sub-total therapies are widely accepted for various malignancies. Focal therapy for prostate cancer is often called the male lumpectomy. Lumpectomy, however , was adopted following nearly 50 years of randomized clinical trial data starting with the transition from the Halsted radical mastectomy.

The successes in breast cancer are largely attributed to the leadership or Bernard Fisher an individual who we badly we need in prostate cancer focal therapy. New data demonstrating metastasis-free survival as a surrogate for overall survival, may, for the first time, make a trial of focal therapy feasible and I think for the rest of the day we will talk about that endpoint and others. So, with that, I would like to say thank you.

[Question from audience, inaudible]

So, I think it depends on the context, right? So, you are absolutely right if you did like they did in the TOOKAD study and said we are going to compare low risk patients for partial ablation vs active surveillance, those curves are going to look completely different than they did in the Fisher trials, right? No one had any events essentially, right? So, it was just about who didn't move on to whole gland therapies.

But, you know, if you select the right patient population, say high intermediate risk or intermediate risk patients – or even some high risk patients with prostate cancer, you could start to have events at a reasonable frequency where you could potentially at 5-8 years, detect differences in overall survival or at least be able to demonstrate equivalency in terms of overall survival at those time points – granted the event rate is low, and Dr. Eggener is going to talk later on about what that event rate is in intermediate risk prostate cancer, but there are events and you can start to detect them.

[Question from audience, inaudible]

And then just a word on multifocality: Dr. Eggener, correct me if I'm wrong, I believe I learned from you that its about 30% multifocality in breast cancer which is much higher than I think many of us presumed, right? Because people who are on the "con" side of

this often argue there is no multifocality in breast cancer and prostate cancer has tons of it but there is actually a quite a bit.

[Comment from audience, inaudible]

Mmhm, that's right. And the real proponents of focal therapy for prostate cancer would say "Yes, so what you have these local recurrences and these out-of-field recurrences, you just ablate those and perhaps you would end up with exact same result, where the eventual outcome is unchanged, resulting in radical therapy."

[Question from the audience, inaudible]

That is a great question. The difference being that we have a systematic way of sampling the prostate. In breast, the sampling techniques are quite different, but yes.

Art Sedrakyan: You know the vision that Mike presented, in my opinion is a big static - RCT to RCT, what happens in between? How do we even come up with those endpoints for an RCT when a new technology , a new approach, is being developed. I think the past has not been well informed by continued static collection of refinements of understanding which endpoints and effectiveness endpoints, safety endpoints you should measure. Before you come up with an RCT you go through the stages of developing the technique adoption and you mature the technology before an RCT happens. And you learn a lot from that RCT until the next RCT. So, I think this static vision does not cover the evolution of technology development. So, the registry mechanism that we are talking about is a way to improve as care is provided right now.

And at the same time, we're thinking that it would be endpoints developed to measure performance and that quality technique is applied in some measure of performance. Ultimately, towards the goal of indication.

And whatever design the group will think is needed for indication - cancer indication is different - then the process we're talking about would get there. And the process we are talking about how to improve the care in the interim. I think we should approach in a more dynamic way, how we think. Rather than think from RCT to RCT, let's get ready, and then in five years or 10 years we'll have the results and we'll change. What happens in 10 years? I think that is little disconnect that we need to address.

[Comment from audience, inaudible]

Jim Hu: Yes, I mean this is briefly to say that I think that - you know, and Charlie

has clarified - and feel free to jump in anytime – I mean I think we are just having an open discussion to help – you know - the different agencies, the different divisions within the agency to think more outside the box and I think that the dynamics of how I think urologists may view the change. I think Dr. Gerome made a great comment in terms of - you know - breast analogy – I have my own personal thoughts about using metastasis as an endpoint which we'll get to.
But to Art's point, I don't think we're necessarily trying to design the trial ourselves – I think we are flushing out what timeline we should look at, what the endpoints would be – but at the same time, understanding that when you are thinking about a trial, for instance, - what is unsaid here, and I think Mike talked about this a little bit in terms of even looking at in-field recurrences, right? If you do an RCT and have guys with either very little experience or poor radiologists out there – you know – 30% of community hospitals don't do prostate MRIs right? And so I think that the real world evidence – you know – there is a room for both.

Danica Marinac-Dabic: I could add a couple of things. From my perspective is – when we are talking about the infrastructure development. The infrastructure of the future that will be flexible enough to match the variety of design and technological approaches. And be receptive to the need for innovation - not just for the device development but also on the surgical technique development.

Things that are part of delivering the actual good 21st century clinical care and in order to do that, there ought to be investments into the national infrastructure for example. If the goal is capturing of endpoints that are needed for today's evaluation, obviously this can be done in the registry. One can envision, you know, future randomized controlled trials being indexed in the same SPARED registry that you guys are developing here.

There is no reason why this module cannot evolve and that can be under the firewalls and be able for industry to be able to think about them and as a better, faster and cheaper ways of collecting the data. But I think it is about thinking broadly. We have an opportunity because our center really invested significant resources in the development of the national evaluation system for health technology, industry bought into concept as well. So I think what are you doing now across various clinical areas promotes the same concept. Now is time to think about investing in infrastructure and later we will be able to make the most of study design.

Charles Viviano: So, it was surprising to some of you, the data that we got. It is probably no surprise that even with a short endpoint, such a metastasis free survival, we didn't get those data either. So the concept of doing a clinical trial, at least initiated by sponsors by manufacturers – if they saw that there is a reasonable east way or a

quicker and easier way of doing that trial to get that indication – we probably would have seen it already. We probably would have seen those data, that trial. The other thing to remember is – as I'm sitting in a room filled with academic urologists. It's one thing for any member of this group to go often to do the study. But none of you can change the indication for the device – only the sponsors can.

Now, you may work with them to make them, they may solicit to work with you and maybe even fund your study – or to work collaboratively, but they have to submit for that change. None of us can do our own study with their devices even though they are on-label now as ablation devices, and then come in and say "I want to change the indication for SonaCare or the Focal One to include treatment of prostate cancer."

So, while it might seem obvious to many of you in the room who are very familiar and comfortable with doing trials and maybe even the randomized control trial that Mike dreams for, and hopes for, that will happen…

Even if that trial gets done – it may not, from the FDA's perspective, just to bring back to us - that doesn't change the indication per se. Now there is a subtle difference here in the room and the first thing that I said at the very first meeting back in July – that Mike nicely had all the dates back in 2008 - was in the SPARED group which came to be called SPARED, it was called something else at that point…

We all have different things, out of this thing, that want. We all have different goals out of it. The FDA: possible change of indication, new devices etc. Academic clinicians: publication, adding to the knowledge base, possibly, clarifying management. So, evaluations to investigate the current management of patients with focal therapy might be different than the studies that would be required to change an indication for the device. So, that is just the thought. I know the workings of the FDA, even though many of you are very familiar and have interacted with the agency - regulatory requirements sometimes get in the way of doing things that seem straightforward. So, I just wanted to put that out there.

[Comment from audience, inaudible].

Yeah that is right. It is being recorded. That is just putting it out there. There might be some room for you know - collecting registry data – because it is really going to be up to the sponsors to collect those data, or to collaborate to get those data in one way shape or form and then come in with a change of indication as either a 510k or something else through our pathways.

So, that is just a thought as to why we still might want to move forward with collecting data in a registry. And if we do collect the data in a CRN, we want to make sure it is the right data and data that can be useful for everyone. Anybody else have anything they want to talk about following on the heels of Mike's talk? You've already introduced Alan.

Alan Priester: Checking, test one. Alright, for those of you who don't know me, I work with Lenny Marks at UCLA, I have been there for 6 years, I got my PhD there on projects for focal therapy, targeted biopsy, and MRI pathology correlation. All of which will covered will be covered at some point in this talk. Next slide.

So, right now, I think we are underutilizing fusion biopsy, which can tell us a lot more than whether or not a target contains cancer and what Gleason grade that target happens to be. A properly optimized fusion biopsy can also optimize candidate selection, margin evaluation, side effect reduction. The real question is: How to craft that pretreatment fusion biopsy and also how to craft margins in a patient specific manner to maximize success while minimizing side effects?
Next slide.

We have two data sources at UCLA that I'll be leveraging for this talk. First is our targeted biopsy database which as of a year ago (these numbers are a little old), had 40,000 cores in 2300 patients all of which were fused with MRI via the artemis system. And we also have a large number of whole mount cases, something like 500. 125 of which are reconstructed in 3D with the help of 3D printed patient specific molds. So we have very accurate correlations there. Next slide.

My first subtopic is going to be fusion biopsy for selection of focal therapy candidates. This is a topic that we looked at at UCLA last year in published paper. Next slide. Dr. Nassiri et al, and I was also a coauthor, reported on a retrospective study of 454 cases that had MRI visible lesions positive for prostatic cancer.

These were sorted into focal therapy eligible and ineligible categories. Eligibility being defined as whether or not the biopsy record showed them to have significant unilateral disease, significance being Gleason 7 or large volume Gleason 6. And, to my surprise anyway, – nearly 40% of men were eligible with the majority of ineligibilities being due to bilateral significant disease. Next slide. Oh, yes.

[Question from the audience, inaudible]

Off the top of my head – I do not know the answer to that – I suspect that a pretty large proportion of them are large volume Gleason 6. But I will get that answer to you later, if you like.

Next slide. So, that was cross referenced with 64 patients who went on to receive radical prostatectomy, which showed which patients truly had bilateral significant disease. The answer was, that fusion biopsy ended up being 75% accurate for predicting focal therapy eligibility.

I think the more relevant figure there though is the specificity, because it is a pretty bad error if a patient receives focal therapy and there is residual disease. Although with proper follow up, perhaps it wouldn't be so bad. I think the question was raised earlier: whether or not residual disease would even reduce survival and I think no one really knows the answer to that.
But at any rate, according to this data – it looks like more than a quarter of patients would be incompletely treated according to the fusion biopsies.

Other interesting points were that about 1/3, 1/3, 1/3 of patients were split between site-specific, quadrant ablation, hemi-ablation and also that targeted cores alone would not have been sufficient for determining focal therapy eligibility. You really do need the systematics because they are the ones that detect bilateral significant disease. Next slide.

This is a study that is unpublished at the moment, it's something I did two weeks ago because it occurred to me that - at least I haven't seen anything published on - at what rates patients progress from focal therapy ineligibility to eligible and then from eligible to ineligible again because of bilateral significant disease. So, this is a study of 401 AS patients from the UCLA database.

On the first biopsy, 83% of them were not eligible because they had clinically insignificant disease. This is not a surprise – this is the AS database where most men have 3+3
After 1-year follow up, 14% progressed to have significant disease where none was observed previously, and another 9% after two years.

So, overall - at some point – a quarter of men in our active surveillance database were, at one point, focal therapy eligible. And the rates of progression to ineligibility because of bilateral significant disease were very similar: 13% in year 1 and 8% in year 2.

If you were to take the serial biopsy as an indication of specificity, the specificity in this population is more like 85% as opposed to the 75% in the Nassiri paper. I think the real specificity of fusion biopsy is probably somewhere between those two figures. But at any rate, this is the rate, I think, at which the disease could be expected to progress. So there is a window of opportunity, I guess, in which patients are focally eligible but eventually will not be. Next slide.

Changing gears – I would like to address the topic of safety margins which we can look at both from the perspective of targeted biopsy and also whole mount. Next slide. So, I performed a study that was presented at the AUA this year, which looked at cases that

had a single biopsy positive ROI. From our biopsy database that was 14,912 cores, and we measured the distance between those cores and the ROI for the positive and negative cores and looked at the trends that resulted. Next slide.

And the trends were pretty distinctive, as one might expect, for targets that were, so - x-axis is distance to the ROI surface, y-axis is probability of any one core detecting cancer. So for cores that were right at the surface, the probability of detecting cancer was high - but of course, as you get farther away from the ROI, that probability tapers. What is really concerning about this, is the fact that it doesn't taper to baseline prostate cancer probability until you are above 15 mm distance from the surface. Which means that if you were to treat these patients with a uniform margin, a 15+ mm margin would be necessary to get a 90% efficacy. Which is not great - because I think in the majority of patients, a 15 mm margin would cross the midline. Next slide.
These results were also supposed by our whole mount database. This is from the paper that I published two years ago: 114 whole mount cases that were registered with those 3D printed molds. Those molds allow us to reconstruct the tumor in the 3D and then correlate it with the ROI position. So, in the images you see here: red is the tumor, green is the original ROI that the radiologist contoured without any knowledge of the whole mount results. And as you can see - especially on the 2D image on the lower left - the extent of the cancer is severely underestimated by ROIs in many cases. Next slide.

So, if you look at the Hausdorff distance, the maximum distance between the ROI and the tumor extension -- even for the subset of the patients that were focal therapy eligible. I believe that was 35 out of the 114. The median distance was 10 mm - meaning that if a 10 mm margin were used, 50% of patients would fail. If you want to reach that, you know - 85%-90% threshold, again you need to get 15 mm or more. Next slide.

So that was the bad news. The good news is, treating with a uniform margin is not strictly necessary and in fact is suboptimal. We also observed in that study that the degree of cancer underestimation was highly correlated with anatomic direction. So, the MRI invisible portion of the cancer tended to be much larger than expected along the base-apex axis, relative to the anterior-posterior or left-right

I think the two big reasons for this is the reduced resolution of MRI on through plane and also the fact that these ROIs are contoured from an axial perspective. So it is more difficult to distinguish the true cancer boundaries out of plane. Next slide.

So, we can leverage this trend. As a proof of concept, I performed a simulation on 20 of those whole mount cases that were respectively focal therapy eligible. And instead of applying a uniform margin like the one seen on the lower right, we applied an anisotropic margin or an asymmetric margin like the one seen in the lower left.

This was done by just basically having it expand more rapidly on the prostate capsule than towards the prostate center (as we have observed many tumors to do). And using

this approach we were able to reduce the mean treated volume from 45%, or nearly hemiablation, to around a third of the prostate volume, while maintaining the same level of efficacy.

So, that was encouraging - but at the end of the day- tricks like this can help you reduce the overall treated volume of healthy tissue, but you still need, I think, to inform treatment on a patient specific basis using pretreatment biopsy. Which takes me to my last topic. Next slide.

The pretreatment planning biopsy, which is something that I haven't seen published in a lot of detailed form, and I haven't formalized my analysis of this, but I will give you my thoughts and my preliminary results on it.

So, it stands to reason and it's intuitive that if a biopsy comes back negative outside the ROI surface, you should treat less in that direction. If the biopsy comes back positive outside the ROI surface you should treat more in that direction.

But in order to make that less of a subjective and more of an objective measure, I proposed a metric calling "M1" for now, which is based on the observation that the ROI target tends to be the metabolic center of the cancer and cancer will extent outward from there.

And so, if you are examining a voxel in yellow there, the most likely path the cancer will take to get there is a straight-line path. However if a negative biopsy lies along that path, the cancer would have to take much more tortuous route to get there.
And the probability of there being cancer at that voxel of interest in yellow is much reduced.

So, the metric is simply, what is the distance between a negative biopsy core and that line that connects the ROI centroid with some voxel that you are interested in measuring.
And we went ahead and measured that metric for about 6,000 cores. Next slide.

And there was a really distinct trend - I think some of this might be artifact - but I think it does reveal a real trend. In that the closer a negative biopsy is to a point, the less likely there is for cancer to lie beyond that.

So the x-axis here is that metric, how is close is the negative biopsy to that line. Y-axis is probability of detecting cancer. What this says is that if a negative biopsy lies within 5 mm of your point of interest, or 5 mm - basically between that and the ROI – you have less than a 5% chance of detecting cancer beyond that point. And this has really interesting ramifications for focal therapy and focal therapy planning biopsy - next slide.

So, what I am proposing, based on this data, and the data I presented previously on the tapering cancer probability based on distance from ROI surfaces, is planning biopsy where the cores are spaced approximately 5mm apart. I think less is better, but this

data seems to suggest that 5mm might be sufficient. And about 10mm radially from the ROI surface.

So that might look something like this for one case. Here you see that there are 6 cores taken in a rough ring around the ROI. Let's say that, hypothetically, four of these cores come back negative (those are the blue one) and four come back positive (those are the red). The margin that would craft in response to this biopsy outcome would be constrained wherever there is a negative core, the data seems to support - you don't to treat beyond that margin. But wherever there is a positive core you need to push that margin out.

So, if you were to have a 10 mm radial line of biopsies around the ROI, you would want to treat at least 5 mm more whenever a core comes back positive. This also has implications for focal therapy follow up. If you did end up treating with that margin, you would want to, I think, follow up with another ring of 5 mm spaced biopsies all around the treated zone to make sure that there was, indeed, no cancer beyond it.

You can also think about other, more involved schemes, like concentric rings or laying down lines of biopsies to prevent treatment of sensitive anatomy. Like if you wanted to avoid treating the urethra here, you could have laid down a line of biopsies along the midline. If they all came back negative, you don't have to treat beyond that point. Now, I am running simulations currently to formalize this analysis, but this is what preliminary result show. Next slide.

So, those are all my key points summarized here. Based on our work with focal therapy eligibility, we verified that targeted and systematic biopsies are needed and patients tend to progress from ineligible to eligible and then from eligible to too much cancer at about a rate of 10% per year, it seems. We found that fusion biopsy seems to have a specificity of somewhere between 75% and 90% depending on the population of patients that you are looking at.

Based on our margin work, we found that prostate cancer extends 15 mm or more from MRI visible lesion - at least if you want to get the majority of cases treated specifically - but it expands anisotropically. So, we shouldn't be doing a uniform margin, we should be expanding it more rapidly towards the capsule and out of plane.

And in my opinion, based on our initial results, an ideal focal therapy planning biopsy would have 5 mm spacing and about 10 mm radially from the ROI. And that concludes my talk.

[Question form audience, inaudible]

Sure. Definitely. So, for our focal therapy follow up cases, we have taken a number of cores from the supposedly treated zone and then generally we take at least 4 cores like around it. Similar to what I described there, but not so formalized. Because we are not able to, a priori, define which biopsy spots we want, using the current focal therapy

systems, Lenny Marks just makes a sort of judgement call on the day of. I would say between 5 and 10 mm radially outwards, usually one in each of the cardinal directions, he will take a biopsy in the margins to see whether or not anything is missed.

I think that, ideally, we should be working with the fusion biopsy manufacturers to be able to define, a priori, which sites we want to sample and then having custom targets at specific locations. But that will have to be in collaboration with industry. But the results that I showed regarding the probability of cancer being beyond that sort of - line of negative biopsies, sort of negative biopsy shadowing effect – I think that applies for follow up is well for preoperative planing.

So, if you have dense enough spacing in a ring around the supposed cancer center, you can be reasonably certain that there is no cancer beyond that. That being said, I think it is a really tricky proposition: doing focal therapy follow up depending on the modality that is used - because the original target is often changed dramatically by treatment, right?

A lot of it will be converted to scar tissue or basically reabsorbed and so even targeting the region that you treated previously, 6 months out, is very very difficult. So, I think that taking more biopsies – yeah there's registration problems – I think taking more biopsies is better than less and we should be airing on the side of caution.

[Question from audience, inaudible]

So initially, it's just the twelve core biopsies - and then usually 3-5 cores from the target itself, not around it - once the patient is identified as a focal therapy eligible candidate - then there is another biopsy session, sort of a pretreatment biopsy, in which you take that ring of cores - I think for a normal sized ROI its between 5 and 7 cores additionally, in that ring around it.

Regarding a question for out of target positive zones, if it appears to be associated with a target - you can just sort of extend that ring to include it. If it is a distinct zone, from the ROI, if it's a truly MRI invisible cancer, I don't think that I would advocate, at this point, focally treating at all. I mean, it has to be MRI visible to be the basis for your center of treatment.

[Comment from audience, inaudible]

So, I totally agree, in terms of MRI quality being crucial and also, I think contouring procedure being crucial - as you can see, even on these images - I think if it had been contoured more aggressively, like it would have been a far lesser margin. Right?

The problem is right now, that they are contouring using the same protocol used for targeted biopsy instead of contouring for focal therapy, right? So, that definitely affected our results. That being said, I think one of the reasons why we found there to be a greater margin than in another groups - is that almost all previous groups have been

looking at the difference between ROIs in the tumor in-plane only, while we were measuring out of plane - actually reconstructing the tumors in 3D.

And we found that the greatest degree of underestimation was in the through plane. Whereas almost no other group has even measured that. Yeah, once it was sliced down, you're just using the 2D radial distance. For us, a lot of them were extending out of plane, like significantly.

So, what you see there - that red blob there - is the result of probably 4 whole mount slides that are serial. And then we sort of stitched together a 3D object based on that. And they were sliced using a slicing guide - a patient-specific 3D printed mold. So, we are pretty sure that those slides were actually taken in parallel and what the spacing between them was.

[Comments from the audience, inaudible]

Charles Viviano: So, I just wanted to pick up on this concept of what the FDA wants and what the community can do. You heard Ben Fisher, the division director, say "we'd love treat and resect data for our ablation tool devices." We don't expect everybody to go out and treat and resect. I think, you know, that's the point I was trying to make earlier. What we might want is as close to the truth as we can get. It does not necessarily mean it translate into what the practice of medicine involves into or is - with regard to the diagnosis, treatment, follow-up care of focal therapy for prostate cancer. That is practice of medicine stuff and we stay out of that.

But we'd like to get as close to the truth for a device as we possibly can. As Johnathan said, we need a reasonable assurance. What that is, is vague. But you know, we'd like to get as close as to the truth as we can, but that doesn't mean that is what would you normally do in community practice or even academic practice.

You are not going to go out and treat and resect all of these guys with Gleason 7, just because that is what they FDA got for its information. We are trying to get the most informed clinical benefit and clinical risk information to you. I am not going to even ask by a show of hands as to how many times you've read the labeling of a device you've ever used or that I have ever read the labelling for a device that I have used. But that said - we try to provide as close to the truth as we feel is reasonably accessible. And is reasonably doable for the population that we serve. I think it just highlights this interesting conversation that we are having as to - we still do not know how to treat people, or men, with focal therapy or how to follow them appropriately.

And the shortcomings that Art mentioned with potential means of following -- it is a little bit of a different question as to what the FDA would want. Now I understand that we are not all here just for what the FDA wants for focal therapy. But as I said earlier - all of us around the table want different things out of this opportunity.

Danica Marinac-Dabic: I'd like to just to say one more thing for what the FDA wants. FDA actually knows very little at the end of the free market period and at the time when the project is approved.

And with all due respect, what FDA wants at the free market - we all recognized, and you hear our center director talking all the time about the actual lack of evidence of how the product performs in the real-world setting.

And this is why this whole shift to real world evidence and increasing access for real world data - and ensuring the continuality of the evidence generation to the extent that we actually reorganized our center totally to erase the boundary of the free market period.

So, what FDA wants is really to be able to have the good, solid infrastructure to continue to learn about the performance - even after certain decisions are made at the time when the technology is introduced into the market.

So, it's really important to kind of understand that the continuity of evidence is what we are building. So, we are going to make certain decisions at the time of the product introduction to the market, based on the best available evidence at that time - but that is really not the… everything that we need to know. And now, as I said, with the reorganization of the center, we will be able to better integrate that evidence to help inform the companies and others as they try to improve the product. So, from my perspective, it is really about having that ability.

Charles Viviano: Thanks Danica. I think we'll move to Fernando. We are well behind on the schedule obviously - we definitely want to try to leave time at the end for the free flow of ideas about what the actual endpoints and study design and registry data elements might be like - So, we will try to somewhat limit comments after the presentations to just a couple. So that we can get to that time at the end where we can really, hopefully get to the crux of the issue. So Fernando, please.

Fernando Bianco: Ok, thank you very much for the invitation to be able to present this data here. Now this will be just data so it's going to be short and to the point. Next slide, please.

We started our protocol about 5 years ago on MRI fusion cryoablation - the eligibility in there is based on the Gleason system - and age – that's how we stratified. But pretty much anybody who was 70 years or older - which is the bulk of the patients and who had a tumor burden seen on MRI, less than 50% were eligible.

On our follow up, the key things is that by the 3rd month we get our first PSA and we also measure flows and residuals and then we measure with a composite of EPIC and IPSS every three months. At a year we want to have a biopsy on every patient - we biopsy them based on MRI fusion - we hit the areas of target, we always sample those, but we also take some randoms. And there are other endpoints to the study. This is all

done in the office setting which effects costs. It decreases or takes away the anesthesia component and the hospital component. Next slide.

So, the key, to echo of some discussion before, is the acquisition of imaging is really what's pivotal. And one of the things we do is really work with places that have good MRI imaging and then we worry less about the interpretation, because once you have good imaging then that can be reviewed by any number of radiologists.

Then we focus on the execution itself - of the biopsy, or treatment, and most the biopsies we do now - because of what we have learned - are done transperineally - again in the office setting under local anesthesia. All the information is captured in an app, that patients have access – and they can just add up survey information. And this also captures when they come to the clinic. Next slide.

This kind of looks at the principle of it. The areas of interest are identified – ideally, in what we call a cycle - there basically are targeted biopsies performed and they are treated and the cycle is concluded a year later when the second biopsy is performed.

The area of interest is sampled and then is proven. And then the treatment is planned with a good margin around it. And the goal is also to have several layers of protection of safety when we do this - the first one being the actual area of interest, the second one being the actual painting of the treatment area and the third one being the actual prostate itself. Next slide.

And these are models of plans of how can they be - and I think one of the advantages of cryoablation is that you can access several areas of the prostate so the multifocality becomes less of a factor than just treating a single area.

This is, I think, different than the traditional focal therapy concept in which you just focus on an area of the prostate. This is more like multifocal or targeted treatment of tumors. Next slide, please. And, basically, we developed a local block, some years back, and we do this in the office setting then we put the needles right at the plans.

The plan is in place once we have the fusion of the MRI with the ultrasound in the transperineal setting. Then we put the needles just like its shown there. Then we advance it, then we monitor them in the real time. I think that, as well, the MRI outline that is monitored in real time, provides a direct feedback in the terms of safety, because you can see the ice ball and as the ice ball distorts the ultrasound image, you still have the reference of the MRI outlined there. So, that gives you more reassurance of what you are doing actually - implementing Next slide, please.

So, between August 2013 and now, we have done 415 patients and for what we are going to talk today, we took away or excluded anyone who had a fusion, salvage procedure, or a whole gland or hemiablation. That left 347 patients, however, 129 of these have been done over the last 12 months so they were not eligible for a biopsy yet,

so we will focus on the 218 patients who had at least 1 year of followup potential in the series. Next slide.

This shows out of these patients basically the mean age being 70-71. You can see the interquartile range is 66-76 and this goes with the eligibility. The median PSA being 8. Prostate volume, numbers of lesions, the median follow up of this group is about 24-25 months.

And the potential follow-up of group is about 33 so we were are very close to what potentially could be and this in part because of having access to the data and really running reports every month and really trying to be on the assertive side - calling patients to come back rather than just waiting for them to show up. The median PSA drop is about 30% after treatment. Next slide.

This shows the biopsy outcomes on 164 patients out of 118 by now. We have 54 patients who declined biopsies, most of them because they had PSA responses in excess of 50% drop and stable, so they are hesitant about this, even though we really want everybody to have it, but none the less.

So, 43 out of those 54 basically had a PSA drop pf more than 50% and that is the way they have not had that. We have 109 patients that are proven negative biopsies, these are fusion biopsies. And then we have about 19 patients with in-field recurrences and 36 patients with out of field recurrence.

Here I broke it down between those patients who were diagnosed through a transrectal biopsy versus transperineal biopsy - the reason being is that, earlier in the program, a lot of these patients came referred from other physicians. And we did our best, basically, integrating the MRI imaging with the biopsy results. Now, that is not what we do. We recommend to have a repeat transperineal biopsy, because it will be more accurate.

We have 38 patients that have required re-treatment. Most of those patients because they have out-field recurrences which were considered new cancer lesions but it is likely that those tumors were there in the first time. And we have converted 15 patients out of this series and roughly 8 of them have gone to radiation and 7 to surgery. About 12 patients have died, not from disease. Next slide.

This an analysis that I couldn’t complete for this meeting but that we had done just a couple of months ago on 151 patients. Once we reached that over 150 endpoint. The interesting part here is that when we look at risk groups on these patients whether they were low risk, intermediate risk or high risk, we see that the positive biopsy rate among them was similar. The approach, clearly from the beginning, we can see a difference between the transperineal and transrectal with the incidence of transperineal being lower than transrectal. And then the indications for the biopsies are placed there. Next slide.

[The remaining 5 minutes of Dr. Fernando Bianco's talk was not recorded]

Charles Viviano: Thanks, that was a nice recap. In the effort to try to more along, let's move on to our next speaker, Tom Polascik. He will give us some observations from his experience with focal cryotherapy.

Thomas Polascik: Hey, I'll try to keep this pretty straightforward and light and focused on some of the conclusions. Next slide please.

So, I think in terms of functional outcomes - really we have proven this across multiple studies even with the single center retrospective studies. Continence has a very strong robust definition of no pad use and 96+ percent reach that, despite whatever kind of template they use or whatever instrument. Potency can vary and I'll speak to the cryo side. Cryo typically uses hemiablation and a 70-90% in general of those previously

[The remaining 10 minutes of Dr. Thomas Polascik's talk was not recorded]

Charnels Viviano: Thanks Tom. Any quick questions?

Just in the interest of time, I'd like to move on to Art.

[Dr. Art Sedrakyan's talk was not recorded]

Charles Viviano: Thanks, Art. Please bring us back to the OPC/OPG concept where we have the open discussion towards the end.

So, I think we are certainly off schedule but it is probably about time to take a break. For those of you who do not know, there are bathrooms just our here to the left. It's almost 3 o'clock, please come back at 3:15, we will continue with our 3 remaining speakers and after that, I am going to ask all of you to start thinking about one or two specific questions.

Back to Dr. Montgomery's point: What role does the randomized clinical trial vs a coordinated registry network play in possibly addressing the issue of a cancer indication from the FDA?

And secondly, if you had to answer this question before you got to leave the building for security folks out front, question being: What is an acceptable endpoint for a device - a focal therapy device - to earn a prostate cancer indication from the FDA. That is what we really want to get down to and discuss before the end of the day, so, please start thinking about that: What - at the end of the day - we have to have reasonable assurance of safety and effectiveness.

The safety part - we are going to get - we will collect all adverse events, we're gonna get that. The effectiveness part has to be clinically relevant when we give a cancer indication. What gives us confidence that whatever these endpoints are, give us the confidence that this merits a treatment for localized prostate cancer.

So, please, while you are taking some coffee, or going to the bathroom or whatever, please think about those questions – 'cause that is what we are really going to get you towards the end, and we are looking forward to speakers to begin at 3:15.

Scott Eggener: If you look at low-risk disease untreated, matched to the population, without prostate cancer, those lines are right on top of each other, and even for intermediate risks, which most places treat, they start diverging in maybe five to six years, and at fifteen years, there's maybe a 5-7% difference, it's not major. The major differences start, obviously, in the high risk for metastatic.

If you look at that middle row there, intermediate risk of prostate cancer, untreated, so no curative intent, I don't know whether it's watchful waiting or true active surveillance, but if you go out 15 years those orange shaded areas, this is basically death from prostate cancer, all ages, and then by age category, but regardless of age, there's about a 20% risk over fifteen years of dying of prostate cancer. It's meaningful, but it's not a very high percentage of men. Most of these men are still going to die of other causes.

Now the Sunnybrook University of Toronto Plastics Series, it's important to contextualize this and most of you in the room know, when he started this, big props to him for being a pioneer, but it was relatively loose entry criteria, relatively loose follow-up, a relatively high bar for intervention. Even in that context, look at the blue numbers on the figure, which is basically Gleason score3+4 with a PSA less than 20, on a relatively loose surveillance protocol and at 10 years, two percent of the guys have metastases. Now you do start to see, which is a common theme, year 10-15, you get 16% of men, and then there is some data even for treated men that even going out 15-20 years you lose more men. Now, the line below that is Gleason 4+3 with a PSA less than 20 and that's a dramatic difference. Most of these men with the long follow-up, many of them were sextant biopsies, there was no MR imaging, there was very little re-staging, two to three years between biopsies, and even in that context, at least the 10 years, the data looks really darn good for the intermediate risk cohort.

This is a lot more data on it, whatever your endpoint of interest is I'll just put it up there. Basically, low risk intermediate risk, out to 10 years, there aren't many events regardless of low risk or intermediate risk, but after 10 years, in the intermediate risk you start to see a drop off.

We talked about PIVOT earlier, it's a highly flawed study but really admirable that they pulled it off and really important data that obviously everyone should know about. Even in a Nihilistic observation, you look at the intermediate risk, and unfortunately this isn't time dependent it's just cumulative incidents, but median follow-up was 12 years, 8-15% basically had a death from prostate cancer, but it's not like it's a large number of men.

Scandinavian trial, important to contextualize, these are mostly palpable tumors, higher PSA's, more meaningful tumor volumes and here with a watchful waiting protocol, you see a lot of events. If you look at the watchful waiting in the box there, intermediate risk, nearly half of the guys have had a metastasis and that's with a median follow up of 13 years. So you've got a whole wide range of meaningful endpoints depending on self-evidence, how you select the guys, how you diagnose and follow them and your threshold for intervention is.

So, let's move on to whole gland treatment. We could spend a whole lot of useless time debating radiation vs surgery – let's just put it out there that they're both reasonable treatment options – there may be some nuanced differences. I basically wanted to go whole gland treatment.

Last year, Chris Kane and myself and a couple of others dove into what is Gleason 7 cancer and what are the variable outcomes, and it is all over the map. This is the widest, most heterogeneous group of prostate cancer patients, in my opinion. And look at those wide ranges of "adverse pathology" or five-year rates of biochemical recurrence. If you look at the data it was exhausting and really depressing. It makes your head spin. There are really indolent Gleason 7 cancers and there are potentially life-threatening ones and everywhere in between.

But for purposes of today I wanted to throw up a bunch of tables that we had in that paper just to give you an idea of many different endpoints on what is out there in the literature. So this is differentiating sort of Gleason grade group 2 versus 3 in the columns, and you can see from pathologic endpoints, upgrading or downgrading, with an understandably expected slight increase in adverse pathology, that you have a primary pattern 4.

Biochemical recurrence, if you look at 3+4, it's basically anywhere between 2% and 20% recurrence rate after radiation or surgery. Gleason 4+3, there's obviously a higher rate of recurrence up to 40% depending on the series. But there's other series that at 10 years there's a 7% chance of recurrence, so again it's all over the map, and it's likely the cohorts and how they were characterized beforehand.

This is a well-known study, it led to the most recent ISUP modification, this is five large academic centers just looking at Gleason score alone, eliminate every other piece of information you have about the patient, and look at biochemical recurrence rates after surgery. So if you have 3+4 there's a 25% risk of recurrence at 10 years. If you have 4+3 there's a 15%(?) risk.

If you get into the nuance of it, this is a time tested, this has been shown over and over. Probably first about 20 years ago by Tom Stamey in JAMA, where a very strong predictor of outcome is the total tumor volume of primary pattern four or five. This is the Martini Clinic, so there's an enormous amount of men, nearly 10,000 men with Gleason 7 after surgery. Full analysis of the prostate. And look at the stepwise approach of what the amount of Gleason 7, it's almost perfect in the spray chart of what it looks like. And really low volume Gleason 7 basically mimics Gleason 6, and really high-volume Gleason 7 mimics Gleason 8, and everywhere in between. Metastasis and death, it's all over the map.

I'm not a huge nomogram guy in daily practice, but it is illustrative for a conversation like this. This is a low-level Gleason 7, relatively low PSA, not palpable, almost no risk of dying with treatment, and then the risk of recurrence after surgery at 10 years is about 15%. So really really favorable outcome.

Within the same Gleason 7 category, here's a guy who's a little bit older, PSA is 19, all 12 cores are Gleason 7, it's palpable; interestingly, it's still a very very low risk of dying after surgery at 15 years, but a near certainty that he's going to recur at some point. And again, everywhere in between.

Here are some outcomes following surgery. These were four huge institutions that put together all their radical prostatectomy data. If you look at row two and row 3, which are Gleason grade group 2 and 3, you don't see a lot of events at year 10 and these are treated men that have had their prostates taken out, you start to see some events at typically 10 to 15 years, and you start to see a fair number of events between year 15 and 20, particularly in that Gleason 3+4 category. So this speaks to something we all know, that this is typically a really drawn out disease process.

I put together a list of within Gleason 7 other really important factors and this is really important for trial design. If you're going to do a randomized trial, which I'm a huge advocate of, and I think we could pull it off, the beauty of randomization is it takes care of known and unknown confounders, but if not, you really have to pay attention to all of the other factors besides your garden variety Gleason 7, and throw them all in the same bucket. And here's a list of things that almost everyone in the room knows about.

There's many different ways of sub-slicing the intermediate risk category. Dr. Carol and his group have looked at whether you have one, two, or three of the factors, you can slice and dice the CAPRA score, the NCCN, you can get into favorable and unfavorable. Essentially, it gets back to the Martini Clinic slide I showed you. You can slice and dice it however you want to find low-threat intermediate risk or high-threat intermediate risk.

And here's a good example, this is over 5,000 men having brachytherapy, at this center in Chicago, and if you take that favorable risk intermediate category and you take it out to 14 years, it basically mimics low-risk disease. This is an enormous number of men with really long follow-up. And this is the same in a surgical series. Jim Wysock and his NYU group looked at low-volume Gleason 7 treated with surgery, and they compared it to Gleason 6 and there was no major difference, or maybe it was pathologic outcome, but basically it mimics typical low-risk disease.

I wanted to throw in some pitfalls or hurdles. I think we get myopic and siloed when we just think of these ordinal categories: 3+4, 4+3, 4+4. There are many examples as you can imagine where actually 3+4 might be worse. You might have a lot more pattern four in a guy diagnosed as 3+4, than someone who has low volume Gleason 8 or very low volume 4+3.

We talked about ISUP 2014, today's Gleason 7 patient may be yesteryear's Gleason 6. So comparing to historical controls is fraught with challenges and the Will Rogers phenomenon. We're in the MRI era, and we don't have a great way of quantifying or

classifying people when you're sending needles directed toward one lesion. Active surveillance series are widely different, and you should know that already.

Less of an issue than the previous four, the influence of the pathologist. There's a relatively small percentage of patients where their diagnosis dramatically changes – there's all sorts of variant histologies that are being appreciated – more cribiform pattern is worse, glomeruloid pattern within pattern 4 is not as bad, but it's important.

I tried to limit the editorializing when it came to study design, I certainly have some feelings on it but I wanted to put that data out there for you to digest.

Behfar Ehdaie: So these 10 slides are going to be an overview of what I think about clinical trial design, stimulate some discussion, talk about what I did for a study that will be coming to the FDA soon about prostate cancer indication, and why I think SPARED is a better approach in the future, and talk about an RCT that we've been fortunate enough to go through task force. That's less relevant to this group, but its relevant to the investigators in this group.

We have to put on different hats for different objectives. I think an FDA label is the goal, but overall, as clinicians as we talk about different levels of evidence, it's because we are thinking about payers, about thought leaders and NCCN guidelines, and obviously our patients. I want to talk about putting a hat on from an FDA label perspective, and talking about whether we can define a better label.

When we talk about biopsy evidence, I want to talk about things we need to think about. The FDA has been involved with genetic biomarkers, and many of these endpoints were based on biopsy endpoints, and as Scott alluded to earlier, our biopsy endpoints we have to think about more critically. This is a paper we published for Memorial when we asked the question: if a patient has a biopsy Gleason 7 prostate cancer who goes on to surgery, and subsequently gets downgraded or stays at Gleason 7 and you have a second patient who's at Gleason 6 who gets upgraded, so that was the endpoint that was used for many genetic markers. We want to make sure patients don't have a hidden Gleason 7. So when you look at that data there's something that's startling. If both of those patients have Gleason 7 on their final pathology, but differences in a clinically relevant endpoint like biochemical recurrence, is 40% different, which tells us our biopsy entry criteria, pathologic endpoints, and biopsy endpoints as a trial can have very different meanings when we try to bring those out to surrogate endpoints. But sometimes this is what we have, but we have to be cognizant of this.

I'll add one more thing to when we speak about biopsy endpoints in single arm trials and RCTs. What have we learned about retrospective studies? Even in the best of hands, and Scott was right on point when he said if you're not going to do an RCT, you have to think about all confounders - this was a study looking at a large amount of patients, over 12,000, in which a patient got sunitinib up front, got surgery, or just got sunitinib for metastatic renal cell carcinoma.

Removing the idea of P value, I think what's relevant here is the effect size. Based on this study, effect size was almost a 50% benefit to getting a cytoreductive nephrectomy. Fast forward. We have an RCT. An RCT demonstrated, not only was

there no benefit, but the effect size was nowhere near 50%. So again, I think the differences between these two studies is again unmeasured confounders, and things that, as we look forward and think about registries, collecting the right information is critical.

So where does that bring us in focal therapy? This is our RCT in men with low-volume Gleason 6, and I won't go into the intricacies of this study, because I think we were all surprised that the progression rate defined as Gleason 4 or higher, at a two year biopsy endpoint for men monitored vs. treated, it even surprised the investigators based on the preset differences they expected based on sample size calculation. But what we see here is with an RCT you can look at a shorter endpoint because those unmeasured confounders will be distributed evenly between each group. So if we see a study that's an RCt we can look at any endpoint that's a short-term endpoint whether it's a surrogate endpoint, whether it's a clinical decisionmaking endpoint, and feel as both clinicians looking at it from an efficacy perspective, and probably from an FDA perspective, that it's an endpoint that has relevance. But going back to Art's point - regarding OPC's and OPG's I think within that we have to look at single arm studies.

So this is what the difference was: we saw a 20% difference in pattern 4. Alluding to the fact that a biopsy endpoint in a randomized trial that shows a significant difference with a large effect size, there's a signal.

So we have this study that we have spoken about already. This is a registry study, looking at men who underwent focal therapy. And when we look at this data we look at five-year endpoints and we see a progression free survival that approaches almost 100%.

But I will point to this table that was disturbing to me. This is the only study in which a prostate cancer treatment outcome measurement in a multi-variate model, Gleason grade falls out as being significant. That tells me that the outcome measurement in this study and the follow up, there is some unmeasured confounders. Why does a low-volume Gleason 7 patient behave very similar to a high volume Gleason 6 patient?

The story doesn't end there. We don't need RCT's and this is a classic example of when an RCT was never needed. This is the study that Scott showed us, men who underwent active surveillance in Dr. Klotz's observational series.

And again, I think what we see here in a single arm study, we see very little outcomes in which we consider it safe, it can change guidelines, it can change how payers look at a treatment option, it impacts decision makers. And the reason is it's such a good outcome. When you look at numbers like 98, 97%, forget about unmeasured confounders. This is good stuff. And we have an entire litany of literature in testicular cancer based on single arm studies, not because we can't do RCT's in testicular cancer, but when you have 99% survival outcomes you don't need an RCT.

So the takeaway from this slide is, when you set the threshold of an OPG an OPC high enough, for non-diagnostic Gleason 7, or whatever endpoint that's being used, not needing treatment long term, if that's high enough, the idea of unmeasured confounders impacting the effect size becomes less important.

And we've seen this, and Dr. Klotz's study, that was an observational cohort study that was not truly active surveillance, if we compare that data to ProtecT which was a $20 million study, which has research study assistance and follow up, if you look at the mortality rate in that study from prostate cancer it's almost the same exactly as what Dr. Klotz's study showed in the observational study. Suggesting that the single arm observational study with a good outcome can be mimicked in an RCT. When you see differences between randomized trials and prostate cancer treatment versus watchful waiting, when you look at the difference in prostate cancer mortality, what we're really seeing is prostate cancer screening. That's the most screened group on the bottom and the least screened group on the top, which suggests that the patient showing up at the initial point of diagnosis, are at different stages, grades, and different points in their natural history. We're dealing with, and the FDA is going to be dealing with, the third group. To be in ProtecT you had to be screened, and that mimics the population of the United States in the current era. And from all that data, we had a guideline change within two years of an observational cohort study.

So this is lessons learned, and this will be a starting point for some discussion. So this is a study, that I'm the national PI for through an investigator initiated study in which a device that needs FDA approval came to the US and said "we want to do a study working with the FDA for a prostate cancer indication." This is a $3.5 million study to accrue 100 patients to get a 24 month endpoint. We have research study assistants at 10 centers across the country, pathologic review, re-review at major centers, we have a data safety monitoring board. Did we need to do all of that, of could we have done all of this in the SPARED registry? I would argue that this trial, with about 80 patients accrued now of 100, which started about 2 years ago, comes to the FDA with the endpoint being we're taking men with Gleason 6/7 cancer, who would not be qualified in 2014/2015 for universal surveillance, and we take these men and make them low volume low risk with imaging with targeting, with this sort of oversight and data, with pathologic re-review, with anything you want to come to you - would this be the starting point of a prostate cancer indication? This will be a question that will be before you in the not so near future. But we shouldn't expect every company to come to you with $3.5 million, open it up to 10 centers, before they bring it to you. I think we could do this through SPARED.

This is the next step, where we want to be. And really, Mike's words were inspirational. Where we are, we do have a randomized controlled trial. Scott Eggener has been instrumental in helping as well. At the GU steering committee, hopefully by the end of the summer, in which we will randomize men with partial gland ablation vs. active surveillance for intermediate risk prostate cancer, agnostic to focal ablative device to really as a first stage study determine if this paradigm can decrease the burden of cancer treatment in these patients with the endpoint being - prevention of radical treatment or primary pattern 4, which we've already discussed is higher risk than our Gleason 3 plus 4 patients. This is an opportunity for not only people in this room who are part of the alliance group at Johns Hopkins, Duke, Mount Sinai and Cornell to be the first steps in moving this forward, but when it comes down to endpoints and randomized trials, the cost associated, we've seen that, we've experienced it, and I think a registry in which we could define these endpoints and move forward would be very helpful.

James Wysock: We'll overview some of our experience with NYU with rolling out what we're all talking about here today as trying to apply the principles that we've been discussing and what some of the learning points that we've had in essentially a registry environment.

This all began at NYU almost 10 years ago when they developed the Smilow Prostate Cancer Center, and this allowed us to incorporate radiology into our practice workflow which really improved the collaboration with radiologists and vastly enhanced our experience with MRI of the prostate which really is the foundation for everything we're doing here. Without the imaging, I don't think focal therapy would be nearly as desirable an approach for any of us. From 2011-2015 that really grew into our targeted biopsy experience using the Artemis, and then there were initial studies performed with radio frequency ablation. Samir Taneja as well as his work on the Phase 2 trial with the TOOKAD molecule, as well as Herb Lepor's work on focal laser ablation, we have since moved that forward into a prospective focal HIFU and cryotherapy registry.

So we are working under some key assumptions. First of all, we are accepting the index lesion hypothesis. It has to be image visible, it has to be confirmed with a targeted biopsy. We are also accepting, much like Hash Ahmed has in the HIFU trial, and I think why you don't see many biopsies in his group is because there is a very high negative predictive value for properly performed multi-parametric MRI. Whether that's true or not remains to be proven and accepted but that remains one of our key assumptions. The other is what's the appropriate treatment margin, what's the clinical target volume that we're looking to confluently ablate and that's very important in terms of what we're talking about from what would be a clinical endpoint.

So we are looking at men who have unilateral disease, they have absence of higher grade disease on their contralateral gland and its confirmed with just a systematic biopsy that's essentially standing as a surrogate for the negative predictive value of the MRI on the contralateral gland. And there are important anatomical considerations depending on your ablation technique in terms of the gland volume, dimensions, disease location and relation to the apex, bladder neck, -certainly in terms of HIFU calcifications are something that you have to pay attention to. And this is something we would mimic: UCL's post-treatment pathway.

And so we have approximately now, been running our registry since 2015, we have about a 90% enrollment, which is an important point, not every man is willing to enroll in a registry as well. We are following SHIM score and IPSS score. And similar to the University College London, we look at PSA kinetics following treatment at 3-6 months in the first year - it starts to spread out into the Q6 months after that, and we get image follow up at 6 months and 2 years with surveillance biopsies required at 6 months and 2 years.

So this is a lessons learned slide, and I think this is an important point. This is the focal laser ablation results, early on, that Herb Lepor published. He did 25 men meeting the criteria I just described and he did biopsies at around 3 months and he had a 96% negative biopsy rate in the ablation zone and only one man had actually disease identified in the ablation zone and that was Gleason dominant pattern 3, Gleason grade group 2.

So that looked very encouraging. But he got a slightly larger cohort he got about 32 men going forward at 2 years, and essentially everyone got biopsied at this point, and now there was a much higher rate of disease detection. There were 8 men who had a positive MRI at two years, all of them had disease detection in the ablation zone, 75% were greater than Gleason 3 + 3.

The remainder of the group, 24 men, had negative MRI's, but the disease detection in that group in the ablation zone was 53%, so there was a significant increase in biopsy detection rate in the ablation zone at 2 years compared to the early biopsy data. And it is actually a fairly high rate of significant disease that we're seeing and that's in the setting of a negative MRI on follow up.

So just to summarize the NYU experiences, early on also in our HIFU there was an early learning curve that we struggled with - and part of that was bolstered by the fact that we did some treatments using guidance from proctors for focal HIFU, and we saw very high early failure on biopsy data at 6 months, even the MRI didn't appear to be different, and we learned that you had to include earlier data with MRI to confirm ablation zone. The re-treatments were performed on many of those early cases and there was still a fairly high positive disease rate in-field at approximately 15%. We're still very early in a lot of this technology adoption, and so we have to be very careful of how an RCT would be rolled out when there's a learning curve involved in the technology. You really need it to be a mature technology for an RCT to be meaningful and so registry is an important way to follow this because these technologies continue to evolve and there are new ones appearing and we're all very much early in the application of these devices. Cryoablation - the data is a little more encouraging, it's probably influenced by our learning with HIFU, but again, all very early and two-year data for HIFU and cryoablation at NYU are still pending.

How to follow these patients and clinical endpoints? I think we've talked about what we need to use for that and one of the areas we're pretty passionate about, you need to combine imaging and biopsy. This is also from Hash Ahmed's group, where they looked at MRI followup after HIFU at 6 months post-treatment, and the positive predictive value for Gleason pattern 4 was about 10%, 32% for any cancer, and the negative predictive value in their group was very high as they report, 98% for any pattern 4. So this is what bolsters our colleagues in London, and they use MRI to rule out disease, significantly. PROMISE trial also supports that, and that's what they really rest a lot of their assumptions on. We're very similar to that but I think the biopsy data that I showed you with the focal laser ablation points to a different story.

Biopsy is critical for follow up assessment, pre and post treatment. The biopsy technique needs to be consistent. You can't use a mapping biopsy afterwards to compare a systematic twelve core biopsy prior to treatment. You've got to have the same biopsy approach taken before and after in order to make a comparison. And that optimal biopsy protocol is undefined. And when do we biopsy? As I showed you, early biopsy data suggests on the focal laser ablation that we were very successful, but when you look back at 2 years with pretty poor outcomes and that speaks to treatment margin. So how do we get an adequate treatment margin? We use a 1 centimeter margin and I think it's debatable whether that's a blanket uniform margin over all

disease but it certainly is an area for active research. And the clinical target volume needs to be confluent and certain technologies may have more confluent ablation than others and that needs to be an endpoint we need to look at.

So my answers to Dr. Viviano's questions would be thus: Is there a space here to do an RCT? And I would say yes; I think a good comparison group might be radiation therapy to a focal group as well as active surveillance.

What are the acceptable endpoints for cancer control? And this I would say the whole point of a focal ablation is to destroy the disease in the ablation zone. Expecting the focal ablation to have a cancer control outcome outside of the focal ablation zone doesn't seem to be an endpoint that we would ever achieve. If you use a biopsy endpoint, and the time period could be defined 1, 2, 5 years who knows but you need to demonstrate, if you're going to seek a cancer control outcome or indication, that in the ablation zone, the cancer is gone. All of it. So I'll put that out and end there, and we can move to discussion.

[The group discussion was not able to be recorded]

End Transcription