

MAN TO MAN – SARASOTA

Prostate Cancer Patient Support

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Man to Man

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Man To Man – Sarasota is a not-for-profit group organized to educate and inform its members on matters concerning prostate cancer. The organization does not dispense medical advice. Meetings are normally held on the fourth Monday at 2 p.m. in Sarasota Memorial Hospital, although exceptions to this schedule do occur. Call the number above for further information.

The complete transcripts of the following edited presentations are available (**via email only**) by contacting Marion Stuart, marion.stuart@cancer.org.

The speaker for the February meeting was Dr. Nancy Price Mendenhall, Medical Director of University of Florida, College of Medicine, and faculty member since 1985. Dr. Mendenhall served as Chair of the Department of Radiation Oncology from 1993-2006 and is a leader in research with extensive experience in group trials. Her published works and articles have appeared in publications including the American Journal of Clinical Oncology and the Journal of the American Medical Association. Dr. Mendenhall is responsible for the day to day clinical operations of the University of Florida Proton Therapy Institute in Jacksonville.

Dr. Mendenhall: Thank you. Man to Man does a wonderful job of making available to you information about the new treatment approaches that we have, but in general, cancer therapies fall into the category of either being systemic or being local. Systemic means that you want a treatment that goes throughout the body, not focused on one area in the body: chemotherapy, hormonal therapy, immunotherapy. In prostate cancer, hormonal therapy is very common and very effective, taking care of cancer cells that may have spread outside the prostate area. We are also starting to use chemotherapy in patients with advanced and high-risk disease. And there is a lot of work that is going on in immunotherapy – the development of vaccines. But local therapy remains critically important in prostate cancer, and it does in most solid malignancies. The two options are surgery or some type of radiation. Radiation is used in more than half of all cancer patients and probably two-thirds of patients with prostate cancer.

There are different kinds of radiation, but we classify radiation as either being delivered externally from a beam outside the patient – a source of radiation outside, an external beam, traveling into the patient, or brachytherapy, where we actually put the radiation sources right in the cancer. In prostate cancer, a very common type of treatment is brachytherapy, where we put seeds containing radioactive isotopes right in the prostate. You have a very active brachytherapy program

here in the Sarasota area. With external beam radiation, that accounts for probably 95% of all radiation that is given. Most of it is actually external beam, generally given with x-rays. These are waves of energy that travel just like other types of electromagnetic radiation. It would be like light or sounds, ultraviolet radiation, microwaves, things like that. But x-rays are the ones that we use in radiation therapy.

The other type of external beam treatment comes from particles. We are talking today about protons. For prostate cancer we use both external beam radiation and brachytherapy, we use x-rays, and now protons.

If we look at what is actually happening in your bodies at the cellular level when an x-ray travels into your tissue, we find the x-ray travels in and bumps into an electron. An electron is a subatomic particle. All matter is made up of atoms and molecules and electrons are a subatomic particle that is in every single atom, in every molecule, in every cell in your body. These x-rays bump into the electrons and when they do, they have so much energy, they dislodge the electron. The electron is knocked out of its orbit. It becomes very active. It interacts with water. The water is so interactive and charged that it can actually break a chemical bond in the DNA, which is the very important part of the cell that governs how that cell acts, how it grows, how it divides. If we get enough breaks in the DNA, that cell will die. If we get a few breaks, that cell may be damaged and it may not function well later on. But, the main mechanism of radiation effectiveness is through the killing of cells by the destruction of DNA. Protons work the exact same way as x-rays.

This is true whether the radiation bumps into an electron in a normal cell or it bumps into an electron in a cancer cell. So that brings us to one of the most important principles in radiation oncology and that is that radiation effects are non-specific. We can do damage not to just a cancer cell, but also to a normal cell, non-specific. And the amount of damage that we do with radiation is related to the dose we give. The higher the radiation dose that we give, the more likely we are going to get rid of the cancer, but also the more likely we are going

to cause a complication. So we have a balancing act there between getting rid of the cancer but not causing a problem for the patient. In radiation oncology we often compromise the radiation dose so that we don't cause a problem for the patient. Even in choosing that dose that we think is going to give the best ration between killing the tumor and causing a problem, sometimes the price of a cure is a complication. That is where protons are important. That is where we have some promise and some advantages and that is what is going to be important in prostate cancer – it is this ratio.

We call this the therapeutic ratio. That is, the probability that we are going to get control of the disease and not cause toxicity that the patient is unhappy with. The best way to improve that therapeutic ratio is to change the radiation dose distribution. We can change the dose. We can change how quickly we give it. We can add agents that seem to protect normal tissues from radiation or seem to make cancer cells more susceptible, but the basic thing that is most important, that we modify where the radiation goes. In other words, we target more accurately. We try to get the entire radiation dose into the target area and as little as possible in the normal tissue. That is the best way to improve the therapeutic ration with radiation therapy. It is like a balancing act. We are always, in any individual patient, weighing the probability that we are going to do what we want to do, get rid of the cancer, versus cause a problem.

To understand the advantages of proton therapy, it is important to understand how these radiation dose distributions happen when we are using external beam radiation. This is a graph of the depth in tissue versus the relative dose. I'm going to stay here just for a second because this is the most important slide in the whole talk today.

This is the distribution of radiation dose in your body. Zero means the skin surface. We have an x-ray beam hitting the patient at skin surface and then traveling deep into tissue to get to some depth where the cancer is. In prostate cancer, the prostate from the side is usually 22 to 28 cm deep in most average-sized men. If we look at an x-ray beam, and here is a high-energy x-ray beam, in the purple, the dotted line, the 22 MV x-rays... the relative dose is really very high at about 2 to 5 cm deep underneath the skin surface. If we are coming in laterally with an x-ray beam aimed at the prostate, then our highest dose is actually going to be in tissues that are only 2 to 5 cm deep, not at 25 cm where the prostate is. So we are going to give a lot higher radiation dose to those tissues on the way to the prostate than we do in the prostate itself. The way we get around this is we add lots of radiation beams coming in from different directions and they all overlap over the target. That is the only way we can get a high enough radiation dose in the prostate and not cause problems in the bladder, in the rectum, and in the hips with x-ray therapy. You aim at the prostate and that radiation beam goes right through you. It does damage all the way through you like a bullet. There is an exit dose and an entrance dose that we have to deal with. In fact, the vast majority of radiation with x-ray therapy – external beam – is deposited outside the targeted area... outside the cancer. That is just the way x-rays are. And there is nothing that we can do about it.

The pattern of dose deposition with protons is really, really different. Protons are particles, they are mass. It would be like a croquet ball as opposed to a beam from a flashlight – energy versus mass. If you take a croquet mallet and you tap the ball, it is going to go a short distance. If you swing back and hit it harder, it is going to go farther. You can predict exactly how far it is going to go by how much energy you put into it. When it has used up all that energy, it stops. What that means for a patient is that we have a pattern of dose deposition that looks like this red line right here. That is called a Brad peak. We had the proton beam coming along here, a little bit of energy being deposited in the tissues, and then it nears the end of the kinetic energy that you have given it, it gives up all of its radiation energy and it stops. There is no exit dose at all whatsoever. So, we aim at the prostate and we don't damage anything behind the prostate, because that beam stopped. And because most of its energy is given up right at the end of the path, we do relatively very little damage on the way in compared to what happens with x-rays. So, now with protons, we have a means for delivering the radiation to the target. And in fact, the vast majority of the radiation actually goes in the target. Whereas with x-ray therapy, with IMRT -- the vast majority of the radiation is actually deposited in the patient, outside the target. What causes complications is the radiation that is in those normal tissues. Now we have a means of getting the radiation to the target with much less exposure to the normal tissues. That begs the question of whether or not we are going to be able to significantly reduce complications with proton therapy over what we can do with x-rays.

In fact, we should be able to see measurable decreases in toxicity and we ought to be able to leverage that decreased toxicity to give higher doses to the cancer and also get high cure rates. So there are two ways that the proton therapy ought to help us. *(Dr. Mendenhall shows several slides of proton therapy used in other malignancies)*

I'm not going to tell you today that proton therapy is the best treatment in all situations in prostate cancer. There is very little data out there that compares one type of treatment in prostate cancer with another. It is a very hard thing to compare those outcomes. All I want you to learn today is that there is the possibility of proton therapy. There is a rationale for it and there is a little bit of data that is very promising.

There are many patients with prostate cancer. There are a lot of important variables that determine which treatment might be best for you. Prostate size, medical conditions, the aggressiveness of the disease. With seeds, we tend to think that the best patients for seed therapy are patients with small prostates and low risk disease, not real aggressive disease. That is true for surgery as well. If we take a patient with too large of a prostate and try to treat him with seeds, we will end up with a lot of complications. The same thing happens with surgery. There are many treatment options, and all can be effective if you choose the right patient. Each of you has specific variables, all very important in determining which of these potential treatments might be best for you.

Sometimes patients will have several good options and then you choose which is most convenient for you. Sometimes the disease is a difficult disease and all of the options may carry some risk with them and you just have to face that.

It is difficult to compare the outcomes in large part because of all these variables. If you look at a surgical series that is a different group of patients from the series of patients that get brachytherapy and that is a different group from the ones that have gotten IMRT. That is why it is hard.

Is there a role for proton therapy given that we have surgery, we have brachytherapy? (*Referring to slide*) This is biochemical disease control in early stage, low risk prostate cancer. Most series uniformly define low-risk disease as having PSA of less than 10 and a Gleason no higher than 6. Once you get into the intermediate and the high risk, the categories switch and some people will include PSAs up to 100 in the high risk, some will cut it off at 40 or 60 or 20. So the low-risk ones are the easiest to try to compare. This is data with x-ray therapy at the M.D. Anderson Cancer Center in Houston. This is a group of patients treated with highly conformal, highly sophisticated x-ray therapy from 1993-1998, so that they now have almost a 10-year observation period. In low-risk disease, they have almost a 90% biochemical cure rate. That is pretty much a gold standard for pre-IMRT x-ray therapy.

This is data coming from a large compilation of programs using brachytherapy. Brachytherapy with or without hormone therapy and with or without some external beam radiation. A large number of patients, almost 2000, and they have a range of 88 to 98% in low-risk disease. Really good results with brachytherapy.

This is IMRT data from Memorial Sloan-Kettering, maybe the premiere IMRT place in the country. We have conformal x-ray therapy, we have brachytherapy, and we have IMRT. We have low-risk disease. These are pretty much patients with a PSA of 10 or less and a Gleason of 6 or less. A pretty uniform group of patients in terms of risk factors. You will see that the control rates are all pretty similar, 85-95%. Intermediate risk, a little bit lower, but the results are good. It is hard to pick out which one is best if all we are looking at is disease control. (*Doctor continues to refer to various slides; these comments have been edited due to space limitations*).

Let's take a look now at these same types of treatment with grade II or higher toxicity. Grade II means something like rectal bleeding and if we have to cauterize it, it is grade II. Then, grade III really gets into the more serious interventions like surgery. So, these are real toxicities and this is dose escalated radiation and again early stage prostate cancer. We have that same M.D. Anderson series now looking at highly conformal sophisticated radiation. We have the IMRT, the same IMRT from Memorial Sloan-Kettering. We have brachytherapy in a little more confined population of patients. This is the radiation therapy oncology group. It is the national cooperative group here in the U.S. They did a study where all the patients were followed very closely, very carefully, and the toxicity was recorded. They had I-125 brachytherapy in addition with some external beam radiation. So, what we see in terms of GI or rectal toxicities is about 7% for grade II and higher with the x-ray therapy from Anderson, about 15% when we have some brachytherapy, and with IMRT at the Memorial Sloan-Kettering, only about 1%. Now these treatments begin to differentiate themselves in terms of toxicity. They are fairly similar in terms of disease control, but fairly different in terms of toxicity. GU toxicities, this would be

things like needing medical management agents to help with urination and things like catheters and things like that. And again, you can see the brachytherapy tends to have a little bit higher complication rate than either the external beam or the IMRT.

Where does proton therapy fit? Here is some data from the Loma Linda Medical University, where they first used proton therapy for prostate cancer in 1991, and the first papers came out in the late 90s for outcomes. Along with Mass General they did a research study of men with prostate cancer, either intermediate risk or low risk. The first part, five weeks, of the treatment was external beam, and then protons for the last part of the treatment. One group of patients got 70 Gy and another group got 79 Gy. The complication rate with M.D. Anderson was something like 26%. After five years the patients with the higher dose had a 91% five-year freedom from failure survival rate versus 79%. Statistically significant. They proved that dose escalation worked. Intermediate risk was 87% versus 75% -- much better results with the higher doses. But was it safe with proton therapy? The answer was yes. With proton therapy you get enough of that dose out of the normal tissues that you can give a higher dose safely without increasing the complication rate. Remember, this was not protons alone; this was only protons for the last 20 to 30% of the treatment. So, just using protons for the boost made it possible to get a much higher control rate without extra toxicity. In fact, in the overall group it was 91%. In the low risk patients, it was 97%. You can't do any better than that. That is about the highest cure rate you are going to be able to get...97% in the low-risk patients.

Putting the Loma Linda series up here, let's compare it with the other types of treatment. We have traditional, conventional radiation here. We have brachytherapy in the RTOG setting. We have IMRT at Memorial Sloan-Kettering Cancer Center. Then we have Loma Linda protons. For GI toxicity, 7%...this is grade III and higher. The white is grade II, the yellow is grade III. We have 7%, 15%, 0.1%, and 0%. GU 4%, 15%, 3%, and 0% for the grade III toxicity. In terms of disease control, remember we have the 88 to 95%; here we have 97% with the protons. Intermediate risk, 87%. So, I think if we are looking both at disease control and toxicity, the combination, which is what really matters to the patient, there is really enough room in prostate cancer that protons can make a difference and I think Loma Linda has proven that.

The nice thing about protons is that there is no prostate size limitation. It doesn't matter whether the prostate is 80 cc or 60 cc or 20 cc. There is no limitation with respect to tumor grade or extent. In fact, with protons, the larger the field that you need to treat, the more normal tissue savings there are. The more normal tissue that you are sparing compared to x-rays. Occasionally we come across a patient that we can't treat with protons because of their particular anatomy or because they've had hip replacements. If they have artificial hips, that interferes with the dosimetry if it is on both sides.

As soon as the data started coming out at Loma Linda, we knew that protons were going to be the next natural step in radiation therapy. We knew from other investigators at the University of Florida and across the country that we weren't going to replace local therapy in the cancer armamen-

taria with systemic therapy anytime soon. We decided at the University of Florida that a proton center would be a boon for patient care at the University of Florida, it could be a regional medical resource for the Southeast, and it could be a platform for clinical and basic research at the University.

Besides our institute, there are four other proton centers in the country: Loma Linda in California, Mass General, Indiana, and M.D. Anderson. We are a not-for-profit organization. Our physicians and physicists are all University of Florida salaried faculty with no incentive to do anything other than learn what the best role of proton therapy is and bring this new technology on board into the cancer armamentaria.

Our guiding principles are that we don't give proton therapy to any patient unless we think it offers them the best therapeutic ratio. We have conventional radiation there, we have brachytherapy, and we have surgery.

We have protocols open right now in prostate. We have completed three studies in prostate cancer, which we will start publishing outcomes next year. We also have protocols in pancreas, nasopharynx, paranasal sinuses, oropharynx, skin cancers that have spread to the brain, sarcomas, lymphomas, lung cancers, and central nervous system. So we have a lot of different kinds of things going on. For more information, go to our website: www.floridaproton.org.

Q: What is the treatment comparability between proton therapy and an IMRT brachytherapy program?

A: It is very similar sometimes. We think, though, that there is so much normal tissue savings that we are probably going to be able to shorten the overall course of treatment. Of our initial three protocols that have been completed, all had 39 treatments. That is the same as what you would get with an IMRT program, 39 to 41 treatments. We don't need brachytherapy, because we are going to the high dose with the proton therapy, but it is very similar. However, in our low and intermediate risk patients, we are now offering a protocol that compresses that treatment to 28 treatments. We think that we can reduce the overall time in prostate cancer treatment by about 25%. We think that it will be as effective or more effective with a shorter duration of treatment. Certainly less expensive and less time consuming for the patients, but that is another alternative.

Q: The outcomes that you showed us today, were those initial treatment?

A: Yes. Everything here was with initial treatments. Now, having said that, we are intrigued with the situation of a biochemical failure after a radical prostatectomy. We are seeing lots of patients who come in having had either a radical prostatectomy or robotic surgery. What happens is that the PSA starts to rise and we know from trials that have been done that if you go ahead and treat when that PSA first starts to rise, you have a much better chance of being able to control the disease and impact survival than if you wait for a clinical problem to develop. So we are in the process right now of developing a specific protocol. We have treated a number of patients and we have learned how to do it. There will, probably within about three or four months, be an IRB approved protocol for the treatment of post-prostatectomy biochemical failure of patients.

Q: Local recurrence?

A: Yes. I am going to rephrase your question a little bit. I think the question you are asking is: Can we use proton therapy after treatment failure with external beam radiation therapy? Loma Linda has done this in some patients and they have not published their outcomes. I am told that they are reasonable, but there is a lot more toxicity. So it isn't our first choice of the way to use these proton slots that we have. We think there is probably a better use for them. But it is an option and we have done a few patients and you will see some outcomes in a few years, but we need to wait and see what happens.

Q: If there is a recurrence, a rise in PSA, how do you find out where the recurrence is?

A: My favorite tool is PET/CT. It isn't perfect but it shows us things that we don't pick up with just plain CT scans or plain MRs or bone scans, or ProstaScint studies.

Q: If you have part of the treatment and you have a time lapse, can you finish the treatment later?

A: We don't like to do that largely because we don't have a good sense of whether we are helping the patient or not. We think the normal tissues have a cumulative amount of radiation that they can handle and recover from. If you have had two-thirds of the treatment, you've already had two-thirds of the damage those normal tissues can handle. However, if you have some cancer that hasn't been eradicated, it has been growing. So you really need the full dose to take care of it. You want to do a full treatment can't because you have that normal tissue toxicity on board. I think most people would not recommend finishing a treatment after an interval.

The speaker for the March meeting was board certified urologist David Spellberg, M.D. Dr. Spellberg is a graduate of Rush Medical School in Chicago and has a urology practice in Naples.

Dr. Spellberg: Today I'm going to talk about HIFU or high intensity focused ultrasound. I got involved with HIFU about two years ago. I don't know if anyone remembers Star Trek, but the nice thing about that show was that a lot of the things that happened there are actually happening now. Dr. McCoy was able to cure people by just putting a probe over their body. We are not there at this point, but I believe we are getting close to this.

HIFU sends high-intensity focused ultrasounds from outside of the body into the body and treats the cancer. It is a non-invasive treatment that uses heat at a temperature of almost 100C, almost at the boiling point of water to melt the tissue. Now as a kid, if you ever went outside with a magnifying glass and you decided to burn ants or burn leaves, this is the same technology, except it is using a probe that is placed into the rectum. By raising the temperature that high, it destroys the tissues. Now only at the tip of that point or right here at this focal point, that is the hottest part of it. Everything else is cooled so the temperature only does it at the point.

This is the machine (*referring to slide*). The probe gets placed into the rectum and the procedure is all done with three-dimensional, color ultrasound that allows us to see the

sphincter, the bladder neck, and the blood vessels where we know the nerves are that control erections. We can give a very precise treatment with minimal risk of incontinence, minimal risk of erectile dysfunction, as long as these erections are working beforehand. We do not seem to traumatize the nerves, so they are usually pretty much like they are at baseline.

(Video begins) This is the probe, in the rectum -- and this is the transducer that sends the high-frequency wave, and this is the focal point. We go point by point by point through the entire prostate and it melts it at each point. Basically we can destroy the entire prostate, leaving everything else intact. HIFU is not new; it started at the University of Indiana in the 1940s and 1950s. It was good technology but there was no sophisticated equipment to allow you to treat certain areas. It wasn't really until the 2000s when the ultrasound was further developed and capable of seeing small amounts of area, such as blood vesicles, that we were able to start using this kind of technology. So in 2004, HIFU treatments for prostate cancer really started.

Just like all treatments for prostate cancer are individualized, what may be good for one patient may not be good for another. When you talk about a localized prostate cancer, there are certain criteria that make HIFU patients better candidates. Ideally you want a localized prostate cancer. You don't really want to treat outside of the prostate because it is not that kind of treatment. This is a non-invasive treatment for localized disease. You want the PSA ideally to be under 10, but that is not necessarily written in stone. You want the Gleason score to be 7 or less so that we are not treating the ultra-aggressive cancers, Gleasons 8, 9, and 10s. If we can get the size of the prostate to be about 40 cc...50cc you can do, but the larger the prostate, the more time the procedure is going to take. The more time it is going to take, then the more time the patient is under anesthesia and complications can arise. For a lot of patients whose prostates are larger, we can actually shrink them with medication, and then they can become candidates for HIFU.

HIFU is a relatively risk-free procedure. Anyone who has recurrent cancer can be a candidate for HIFU. It can be used for patients who have had radiation and failed, patients who have had cryotherapy and failed, patients who have had their prostates removed. A lot of times when your prostate is removed there may be a little nodule that will form or maybe there will be some growth of tissue. Those men will be candidates for HIFU because you could melt those nodes. For microscopic disease this is not going to work; we have to see something to be able to melt it. Patients who have had radiation seeds and failed, even patients who have had HIFU, if it ever comes back, you can retreat them. There is no limit on how many times you can go through it, and it doesn't seem to cause any damage outside of the prostate.

Over 7000 patients have been treated with HIFU, with about 250 physicians doing the procedure. There are about 100 different centers outside of the United States. There are about 20 physicians like myself who are able to be a facilitator and train other physicians how to do the procedure. It is starting to grow.

The procedure itself lasts anywhere from one to four hours, based on the size of the prostate. The larger the pros-

tate, the more time it takes. It is done typically under a spinal anesthesia so the patient is awake and numb from the waist down. Once the procedure is over the patient wakes up quickly and feels good that night, usually resuming their activity within a day or two. I have been taking my patients to Mexico, and I will get into that in a minute, but the patients will usually have their treatment in the morning. Later that afternoon, they are up walking around. I usually see them in the hotel lobby having dinner that night. Patients bounce back very quickly with the HIFU treatment.

Patients have a suprapubic catheter following the treatment, a small tube that goes just below the belly button with a little faucet on the end and you can tuck it in your underwear. If you have swelling and difficulty passing urine through the penis, you hit the little release valve, it drains, and you close it, and put it back in your underwear. That usually stays in for about one to two weeks after the procedure. Side effects and complications are minimal compared to other treatment options. Frequency of urination, urgency, mostly from the inflammation that occurs from the treatment -- these symptoms generally clear up in a week or two. The tube is out and patients are feeling like they are back to their baseline.

Some of the first studies using the Ablatherm machine showed side effects of strictures, urinary retention, leakage, erectile function, and fistulas. But with the Sonablate, the new generation machine, we are not seeing any of these kinds of complications, probably less than 1 or 2%.

(Refers to slide) This was an independent study that looked at the results in data out there on all the different treatment options, done by a third party who had no financial interest other than what the outcomes were. With surgery, incontinence can be anywhere from 4% to 34%. This did not include the robotic data, but now we are finding out that the robotic data is not necessarily true. Their incontinence rate is maybe a little bit worse than the open procedure. 51% to 80% of men who have had their prostates removed are complaining of some type of erectile dysfunction. A lot of that depends on the definition of erectile dysfunction that you are using. If you use a true definition of being able to perform when you want to perform with sufficient enough erection to maintain penetration, then you are looking at somewhere around 51%-80%. If you start looking at the other types of treatments, there is radiation. Erectile dysfunction ranges from 4 to 10% in some studies. Now we're getting all kinds of side effects. When we look at HIFU the incontinence rate is less than 2% and the erectile dysfunction, they are saying 20%-30%, but again we are using some of the data from the Ablatherm where they were having higher results because their prostates were smaller, they weren't able to treat as big and they tried to treat patients who shouldn't have been treated.

Video on the Sonablate 500 system begins:

"The Sonablate 500 system is a computer-controlled device designed for transrectal delivery of high-intensity ultrasound energy to the prostate for the treatment of prostate disease. Urologists have been using the Sonablate 500 system to treat benign prostatic hyperplasia, also known as BPH, localized

prostate cancer, and recurrent prostate cancer. The device makes use of integrated biplane or ultrasound imaging for real-time treatment monitoring, treatment planning, and pre-imposed treatment imaging of the prostate. Similar to what happens when sunlight is focused through a magnifying lens, precise focusing of ultrasound energy during HIFU treatment elevates the temperature of the tissue in the focal zone very rapidly while intervening tissue between the transducer and the focal zone is kept at a safe temperature. The result is an accurate and repeatable lesion at the target sites that are monitored in real time by the treating physician. All the treatment zones are preplanned and checked by the physician prior to the starting the HIFU treatment. The imaging capabilities of the technology allow for identification of vital structures, such as the prostate capsule, seminal vesicles, rectal wall, the physiological location of the neurovascular bundles. The addition of an integrated Doppler feature into the transrectal treatment probe adds an additional safeguard during treatment. The integrated Doppler feature will assist the physician in the identification of vital structures that need to be preserved in order to avoid problems with urinary continence and sexual function.”

Dr. Spellberg: HIFU is interesting because it has been in Europe, China, Japan, for 12 or 15 years. It has been used more and more. When it was about to come to this country about four years ago, I truly believe that some of the radiation oncologists banded together and were able to convince the FDA not to bring it here yet. One of the reasons was because in Europe, patients were choosing this over radiation treatment. If you look at the number one medical expenditure of Medicare in this country, radiation of the prostate and radiation of the breast are at the top. You are talking billions of dollars. So it seems to me that's one of the reasons that of all the treatments that ever have been given for prostate cancer, HIFU was the only one that was told by the FDA you have to do more testing. Cryotherapy came out, no problem. Robotic surgery came out, no problem. Radiation seeds came out, no problem. No one ever had any concerns. But HIFU all of a sudden, people are concerned about it. In Europe, Canada, Mexico, and the Bahamas, patients are having it done. They are having it done more and more and it is growing. I believe it will be approved here eventually. There are some centers in this country that are test centers. The FDA told the company they could establish some test centers and compare HIFU and cryosurgery. As that became public knowledge, they filled up every single arm of the HIFU treatments within just a matter of a few weeks, but no one wanted to sign up for the cryo section. So those studies stalled. Now there is a study out that allows patients who have had radiation failures to enroll into the test centers. So I believe within the next year or two we are going to see HIFU in our country. But for patients who need treatments now, we are usually going down to the Bahamas. We were doing a lot in Cancun, but Mexico is sort of questionable as far as travel. Cancun is definitely better than Puerto Vallarta as far as safety, but again, the Bahamas have really

taken off as far as the number one treatment location now. Canada can be, too, but from Florida to Canada, it is a long trip and you don't get too many people who want to go to Canada in the winter months. I sure don't.

Basically, this is the disclaimer. HIFU is not approved for use in the United States unless there is a test center and you are part of that testing. So what we do is bring patients to the countries, do the treatment there, and then come back. Why would you go somewhere else for your treatment? I was a little leery about that too. But what I found was very interesting. When you go to the hospitals in Mexico, most of them are privately owned. They are actually nicer than the Naples hospitals that I am in. Every hospital in Mexico is brand new and clean. The company offers the service, so you get picked up from the hotel. You get taken by van to the hospital. You get treatment. You get placed in the van. You get taken back to the hotel. There is a full-time nurse who is always available in the hotel. Patients typically go home the next day and see their physicians back here in this country.

There are more and more patients now who are advocates of this treatment. In my practice we have many patients who are more than happy to talk to other patients about prostate cancer treatment with their HIFU and share their experience. A good place to go for more information is to the website www.internationalhifu.com.

Q: How do you get paid and how much?

A: As a physician, I am paid by the company. So, the patient pays the company \$25,000 and that includes the treatment, the anesthesia, everything. I then get paid about \$2000 by the company to do the procedure.

Q: It is not paid by private insurance?

A: Private insurance actually has reimbursed patients. Medicare doesn't pay for it because it is not approved by the FDA. So patients will pay out of their pocket unless they have private insurance. Interesting thing about private insurance is that I have had Blue Cross patients, I have had United Healthcare patients...now they are not Medicare at all, just private...they have been reimbursed from their insurance companies \$23,000, one showed me because he had a \$2,000 deductible. Another one got \$24,000. So the private insurances are paying for it but if Medicare has anything to do with it, they won't.

Q: Do you travel to these places and have there been any recurrences?

A: Yes, I do travel. I usually go once or twice a month depending on how many patients there are. I try to treat on Saturdays and Sundays, so that the week isn't too bad and this way the patients actually get reduced rates at the hotel. It seems to work out well and then I see them back in the office when we come back in the beginning of the week. As far as recurrence rates, right now the longest study at 12 years shows a 3% recurrence rate with HIFU patients.

Q: How many patients are involved in this study?

A: In that study, there were 600 patients. 91% of the patients at three years had undetectable PSAs and 87% at three years, showed when they biopsied their prostate, they couldn't find anything that was recognized as normal tissue. It was all destroyed...dead tissue.

Q: Low PSAs as well?

A: Their PSAs mimicked the PSAs you would find following prostate surgery. So, their PSAs are at 0.1 and less than 0.1.

Q: Can this treatment be used at other sites other than the prostate, like in lymph nodes and how does it compare to cryo?

A: Again, this is for localized prostate cancer, so we treat the prostate. We have not treated any kind of lymph nodes or anything like that. It is just for the prostate. As far as cryo, this is very similar, as cryo is freezing, this is heating. I think this HIFU is less invasive.

Q: Just as they can use focalized in cryo, can you also just focalize and not do the entire prostate, but just one specific area?

A: Yes, you could. Right now, because of the FDA approval process, we are not doing focal therapy. We are recommending treating the entire gland, because they want to try and get this treatment procedure approved. But the future of HIFU, I believe, is going to be focal therapy because it can be redone so easily. Focal therapy could be done in the office with a local.

Q: Does the image that you have from the ultrasound while you are doing the procedure, is that in real time and then what is your margin of control? Also, in one of your slides, you showed MRI and you used that to show where the cancer is. I have never seen any MRI or read any MRI that could definitively define where the cancer is located in. So, how do you know where the cancer is?

A: The first question was is it in real time? The answer is yes. We plan it in real time and are constantly changing as we are doing it. As to your third question, how did I know that the cancer is there? No, we don't usually use the MRI to find those kinds of things, I just happened to know that he was biopsied, he had a little nodule there, and it was just a really nice picture that was taken so I used it as an illustration. We use the ultrasound and biopsy of the prostate to diagnose. Your second question referring to margin of control. Basically, the focal point is 6 mm up and down and 3 mm across. So it is 1.5 mm margin. Using the Doppler ultrasound real time, we can get very close to the neurovascular bundles without injuring those nerves.

Q: What if you had microscopic disease just beyond the prostate?

A: Well, again, that is why we try and sort of stick with the localized prostate cancer. If we know that there is a lot of cancer on the one side, we can go past that margin and still treat. We can tailor the treatment towards each individual's pathology. When I am doing the treatment, I usually have the picture of their biopsies and I usually do 12 sectionals, so I know exactly where the cancers are. I will probably cheat on the side if there is cancer on the one side and not cheat so much on the other if it isn't there.

Q: Also, related to that MRI image that you showed, what is it that fills in, eventually, that empty spot that you showed us?

A: If you have ever had a friend or family member who has gone a rotor-rooter procedure of their prostate, which is called a transurethral resection of the prostate. This is where we place a small telescope through the penis and we actually scrape out the inside of the prostate to open up the passage way. It is done primarily for benign disease of the prostate. What happens is the whole lining then forms a new passage-way. Well, it looks like that. What happens is HIFU has destroyed the tissue and the tissue just sort of evaporates and you have an open cavity. It looks like you had a TURP of the prostate.

Q: Has anyone had impotence with the new HIFU technology?

A: I am not going to say no one hasn't. If they are having erections beforehand, they are going to have the same erections afterwards. If they are having any problems beforehand, I am not going to say that this is going to prevent any further problems. But we are lucky in this day and age. We have a lot of medications. We have lots of ways of inducing erections. So it has not been as much of a problem if someone is already having a little difficulty, we can usually keep them in the same spot. If they do have some extensive disease on one side, I will usually treat outside there just to make sure that we are getting the cancer, because that our first goal is to treat the cancer.

Walter Reed Army Medical Center offers HIFU for qualifying men with locally recurring prostate cancer in a Phase III Clinical Trial. They issued a press release on March 16th this year. This is in Charlotte, North Carolina with the company, Sonablate, that deals with this. It is certainly a very reliable, reputable place in the United States, so if you're interested you might want to read the article. Again, the study is for men who have a recurrence after external radiation treatment. Thank you.

Upcoming topics for Man-to-Man meetings in 2009 include Robotic Surgery, Supplements and Vitamins, Radiation Oncology, Medical Oncology, and information from prostate cancer survivors as to their outcomes after recurrence. Call the local American Cancer Society for more info at (941) 365-2858.

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