

# 2009 Man-to-Man Symposium

## January 11, 2009

### **Paul Zatz - Host:**

Welcome to the Second James F. Mullen Symposium on Prostate Cancer Recurrence. My name is Paul Zatz, facilitator for the Sarasota Man-to-Man organization under the auspices of the American Cancer Society. This free symposium is sponsored by the American Cancer Society and others in your program that have made it possible.

I am a husband of 48-plus years with a loving wife, who is just distributing the programs. I have five grandchildren, one more than the last symposium. And, I am a 13-year prostate cancer survivor.

We are proud to hold this symposium and hope you have a rewarding and enlightening day.

Some housekeeping things: if you haven't done it already, please check now, turn off the cell phones and the pagers, please, check. Thank you. Restroom locations, out the door, turn left. I hear those cell phones going off, thank you. Out the door to your left there are a set of restrooms. If they are full, you have to go to the hallway and go all the way down past the elevators and there is another set of restrooms.

Please keep the room clean. We want to be invited back. Sarasota Memorial Hospital gives us this facility to use not only for this symposium, but for all of our Man-to-Man meetings. So, please keep it clean. If you have any trash, garbage, etc., please deposit it in the trash cans at the front. It would be greatly appreciated.

How many people here from Sarasota today? Raise your hand. Pretty good. How many people from Venice? Marvelous. Anybody from Charlotte county? How about just anybody else in Florida. Look at this, look at this, from other places in Florida. Anybody from out of the country? Don't laugh. Last time there was a guy here from France. He didn't come special, but he happened to be around and he came to the symposium. I know we have some people here from Daytona. Where are you? Because you called me. There are you, right there, people from Daytona, up over there, terrific. We are glad you are here and we hope you have a great day.

This event will be recorded. It is going to be audio recorded and it is going to be video recorded as well. The video recording will be available on a DVD that will be available. The information in your program that you can buy for \$10. That information is in your program. The audio part of it we hope to eventually have it transcribed and it will be part of our Man-to-Man newsletter that we send out around the country.

Please visit the sponsors of this event in the other room. That is the old board room right behind me. The people who are here with various information about not only their products, but their services and what they can help you do.

After the event, we are going to have a raffle. I am encouraging you, there is an evaluation form in your booklet. If you fill out the evaluation form and turn it in at the end, we are going to have a raffle for a number of books that have been donated by Ed Weinsburg, by 21<sup>st</sup> Century Oncology, by the Dattoli group, by Dr. Myers group. We will have a number of those, I think there is about a dozen books available or more that we will give out at the end.

Upcoming programs for the Sarasota Man-to-Man... in February, we are going to have people down from Shands Hospital on proton beam. In March, we are going to have HIFU. HIFU is not a karate exhibition. That is March. In April, we are going to have sex, I am sorry, we are going to have a program on sexuality. Then in May, we have our panel of survivors that is hosted and moderated by our medical advisor, Dr. Treiman.

I would like you to know that all of our speakers who are here today are here without any charge. They did not charge us to be here and we greatly appreciate them giving up their time and their expertise for us this morning. We do, however, have some contribution boxes around. We would appreciate, if you can, there is one on this table and one by the coffee, to leave us a little something to help defray some of our costs. Some of these things were donated and other people did help out in terms of the expenses, but we can always use a little extra money.

Some thank yous, and I hope I cover everyone here... the committee. The committee made up... if the committee is in here, if you would stand so they can see you, please. Art Iverson, Marion Stewart, Jenya Carnahan, Dr. Allen Treiman, Dennis Welch, who is not here, Darwin Lloyd, Meg Brockett, and Jan Manurite, who is not able to be here today either. Thank you.

The volunteers who were registering you and helping out in here with all the things this morning were organized by Art Iverson. Art, I really appreciate what you have done here.

Though she is not here this morning, we would like to thank Joan Gattus from the Sarasota Memorial Hospital, who made all the arrangements for the tables and the room and everything else here today. We really appreciate all she has done.

Our sponsors...the Dattoli Cancer Foundation, American Cancer Society, 21<sup>st</sup> Century Oncology/Urology Associates, Dr. Myers group, which is the Foundation for Cancer Research and Education, Theuragenics, Endicare, Whole Foods, and the Prostate Cancer Research Institute. We really appreciate their contributions in-kind and in money.

We are going to go over the program just briefly, which you have. We will begin with Dr. Treiman, who will give us a brief overview of the problem of recurrence of prostate cancer. It will be followed by Dr. Myers' talk, and then there will be a break and at that time, you can get some more coffee and bagels and whatever that is there. After the break, we will have Dr. Dattoli speak to us and then Dr. Barzel, followed by a panel discussion. The panel discussion will be questions and answers. You have received some cards there and you can write your questions out and we will collect the questions and Dr. Treiman will be handling the questions to the panel. If you are interested in the Vitas Aval of our presenters, just look in the booklet. You will see very impressive education and experience of everyone who is speaking here today. After the event is over, some of the doctors may remain. Some may not. If not, don't harass, harry, or harangue them in any way, please. It would be appreciated. We have to respect their privacy if they do want to leave. If they want to remain and answer your questions, well and good, but they are not here to give you consultations. If you want consultations, please make an appointment with their office.

The question/answer period, I would suggest that your questions be specific, they be brief. Do not mention doctors by name. Don't give your case history. Address your questions to a specific doctor or to the panel at large. Please, no doctor testimonials, that is appreciated. You can keep notes in the book that is there and because some of the questions, as you go along you might write, and some of the questions may be answered, but by other doctors during this time.

I would like to also tell you that this is a Jim Mullen event. I want to talk to you just briefly about Jim Mullen. Jim Mullen was one of the founders of Man-to-Man here in Sarasota. Though he wasn't among the original six, in 1989, he put it together, he was a survivor himself, he has passed away since. In 1994, he had this group join up with the American Cancer Society. He was a natural leader, an excellent organizer, and a wonderful individual. I did not have the

opportunity to know him personally. His experience in WWII as a Marine Officer, I am sure, held him in good stead in putting this group together. I would also like you to know that Dr. Treiman was there at the beginning, too, and has been the medical advisor to that group ever since its inception.

I would like to recognize also one of the other people, though Boise Coppinger is not with us here today. Peter Stoltz, he is one of the originals. Wave your hand, Peter. I appreciate your being here today.

I have one more thing to say. Somebody gave me this and it happened to be Boise Coppinger. In 2005, a man by the name of Marvin Plusser died. He had told this story how in April of 1990, he had been told that he had three months to live. He had been diagnosed with prostate cancer at Sloan Kettering. He had six months to live, rather. He came to a meeting and he opened up a suitcase and showed us all the reading he had been doing and told us how he was strengthening his immune system with diet, herbs, and vitamins. He was so enthusiastic that he infected the whole room. When another man said he had a short time to live, Marvin jumped up and hollered at him, "You take that cancer, put it in your mouth. Shake it like a dog shakes a rat until it is dead." It scared the hell out of me, but I never forgot how sure he was that he would outlive the predictions, which he did for 15 more years.

I would like to introduce to you at this time our moderator. I would like to say a couple of words about him. Besides his being our medical advisor and being on the committee, he is a graduate of Franklin and Marshall, Duke University Medical School, New York Hospital, Cornell Medical Center, Memorial Sloan-Kettering, Clinical Professor of Urology at Tufts, Board Certified in Urology, and he has been selected as the top urologist in Sarasota and Manatee County by Cassell, Conley Medical...Dr. Treiman.

**Dr. Treiman –**

Thank you all for coming. When I was going through my files and archives and looking at the old Man-to-Man material I had, I found that this is actually the 20<sup>th</sup> Anniversary of Man-to-Man. It started with a couple of patients approaching me. We went up to a little conference room up on the 7<sup>th</sup> floor, which was the oncology floor and we had a meeting. I must admit, I never had the vision that it would turn into anything other than a little meeting once a month with me and about 10 or 15 patients. It quickly became a conference room and then this auditorium. The true genius of Jim Mullen was this booklet. What he did was he put together a template to do

this anywhere in the country. From little ole Sarasota, we went forth and prospered. Men would go north for the summers and they would start their own group. Before we knew it, there were about 50 or 60 groups around the country.

I was speaking to a friend of mine, Jerry Chodak, who is a professor at the University of Chicago, a well-known researcher in prostate cancer. He was very proud that he had started a Man-to-Man group in the University of Chicago. I humbly informed him that we started it here in Sarasota. I still don't think he believes me. In any event, that is how it all started.

This is my autographed copy of the handbook that Jim Mullen gave me and it is dated 1993, I believe, and at that point, there were 560 members in Sarasota and I think I can't even read it there, but about 39 support groups around the country and it grew to many, many more. I suspect there is probably over 100 at this point. Jim was quite a guy. I learned a lot from him. I learned that focusing on a problem and just rallying all the troops around you, as he probably did when he survived Guedel canal, which he did as a marine, you can come up with something that we have here today. After 20 years, it is very gratifying to be here and we dedicate this to his memory.

My job today is to just give a quick overview and let our panel of experts take over. The big problem that we face today is a recurrence of prostate cancer. What I want to do is just through a couple of definitions. It is always good to define things. We are going to hear things over and over again from our speakers. Hopefully, you will get it by the end and if not, we have a question and answer period.

First of all, I want to define a couple of terms about what we are talking about when cancer recurs, prostate cancer. You will hear a term, biochemical failure. That really refers to a rise in PSA. I actually straddle the PSA era. I am old enough to remember before we had PSA. Before we had PSA, when a man had his prostate cancer recur, usually he would present with bone pain, symptoms of problems with urination. We would look into it a little further with an x-ray and find the problem. Now we have this wonderful test called PSA, which finds the cancer early, hopefully, before treatment and then if it does recur at an early point after treatment.

The local failure has to do with the cancer having spread around the gland. If we remove a prostate and the cancer comes back locally, that is in what we call the prostatic fossa or in the region of the bladder or urethra, that is considered a local failure of treatment.

Finally, a systemic failure, obviously, is when the cancer has spread to some other parts of the body, such as the lymph nodes or bones. We will be talking about imaging and ways of finding this.

Again, in the early 1990s when PSA was developed, it changed the whole way we looked at prostate cancer in many ways, including the recurrence of prostate cancer. We get these low levels of PSA return after either radiation, surgery, or hormonal therapy, it would be a tip off that the cancer is back way before any clinical symptoms. My patients would come and say I feel fine, I feel great. I have no problems, but my PSA is going up. And that is really the crux of the problem that we are having today.

The other thing is that we were very successful in finding prostate cancer at an earlier stage and at younger ages, so we have this whole group, and younger I put in quotes, because young in Sarasota is about 85. It is true. I will have days in the office where I will see five or six guys over the age of 90. And they are still playing tennis and I quit when I was 42. We have a lot of younger patients who retreated, men in their 50s and 60s, who 15 years later are starting to have a rise in their PSA. And that is a big group of people. We are talking about 50,000 or more men per year and that is accruing every year over the last 20 years of the PSA era.

So, what does that cause? What I call PSA anxiety. I don't think I am the author of that term, but I see it every day. We are always looking over our shoulders, this fellow is, at our PSA. Everybody sweats their PSA. I don't have prostate cancer and I sweat it when I get it every year. Everybody wants to know what their PSA is. And a prostate cancer survivor, it is especially important that PSA stays down. And when it doesn't, there is that shark or elephant in the room when they come to see me.

Just a list of things that we are going to talk about today in terms of the significance of a rise in PSA. Obviously, PSA anxiety leads to a lot of emotional stress, but a lot of times the first thing the patient asks, "Is the lab wrong? Could it be a problem?" Yes, I have had patients who came in with a rise in PSA only to repeat it and find that it is still 0 or unmeasurable. So, yes, lab errors do occur.

I don't know if you saw the news report that Quest Diagnostics just wrote a letter to thousands of doctors saying that their Vitamin D was wrong. I just had one two weeks ago and I have to make sure that I am on the right drugs. Any test could have a lab error. We will usually repeat the test and that is very simple.

What actually defines recurrence of prostate cancer, especially a biochemical, a rise in the PSA recurrence after surgery, radiation, cryo? There are criteria for that and I am sure that our speakers will go through that. There is obviously different criteria for surgery versus radiation. For example, after surgery, you don't have a prostate so your PSA should be 0. Obviously, after radiation, you do have a prostate, the PSA will have some measurable level in many cases. So, the criteria are different in terms of what a recurrence actually means.

Is the PSA rise from benign or malignant tissue? When we do a radical prostatectomy and we remove the prostate, we might leave a couple of prostate glands behind. Obviously after a seed implant or brachytherapy, you still have your prostate, so there can be some measurable PSA from that.

Is the PSA rise from a local or distant recurrence, as we defined earlier, is it because the prostate cancer is back in the prostate or in a lymph node? That is an important criteria in terms of future treatment.

What is the value of additional imaging tests? All of our panel today will be discussing the new and exciting ways that we are looking at prostate cancer with newer diagnostic imaging tests to try to find small cancers in the lymph nodes or other parts of the prostate.

This is the big one. Obviously, the patient will always ask me, well, now that my PSA is rising after treatment, what is my prognosis? How long do I have to live? Is this dangerous to me? What does it mean? This is the big question that we are trying to answer. We won't be able to answer it today, but in part, hopefully, see the process that we through to try to answer that question.

Another big question, is any treatment necessary? Not always. We will talk about watchful waiting as well as all the other types of treatment options.

Finally, what reasonable options for you as a patient. In other words, based on your age, the type of cancer, how you retreated before. What type of algorithm or thought process did we use to get to that treatment option.

One of the big landmark studies that helped us answer that prognosis question was done by the group at Johns Hopkins in the late 90s. If you know anything about the history of prostate cancer, Dr. Pat Walsh was the fellow who did all the research for the nerve sparing radical prostatectomy and starting in the early 80s, did a huge number of these operations. In 1999, they published this landmark study... actually I don't know why he didn't wait until 2000, but he had

1997 patients...and this up until 1997, so think that is what he was doing. But, over the course of 15 years from 1982 to 1997, he accrued this many patients. One surgeon. This is a study of one guy doing the work. None of these patients were treated with hormonal therapy after their PSA went up. So, it was a very pure study for the time. What they wanted to do was look and see from the time someone recurs after having surgery to the time that they develop metastasis to the time of death, how long does that take, so that we can give the patient an idea of their prognosis and gain some other information as to what factors we could look at to help determine that prognosis. So, what they did is they looked at all these patients. They had about 315 patients that had a rise of their PSA up to 0.2 from 0. That took a median of only about 2.3 years. This is a very high-risk group. Two-thirds of these patients on pathology had cancer outside their prostate. Over a quarter of them actually had positive lymph nodes. So, this was a very high-risk group of patients. This is the median time to the rise. There were about 315 patients or about 15%. It took another eight years on average for the patient to develop a metastatic focus, either in a bone or a lymph node. That was 103 patients. It took another average of five years until the patients who had lymph node or bone metastasis died from prostate cancer and of those, only 44 patients of this group died. It all boiled down to 44 patients out of 1997 actually died. So, when you start doing the numbers here, we are talking over 15 years from the time the PSA started to go up, on average, until the time someone died from their prostate cancer. Now, keep in mind, only a small portion of these patients actually died.

This study has been undated every couple of years and now they are up to over 5,000 patients. They are finding that in the later patients who were found earlier with prostate cancer, that they haven't even met the median survival yet in that group of patients. It is over 16 years. That is a very encouraging outcome from this study. The other important things that came out of this study was the fact that they were able to find what predictors they could use based on what they were finding in the laboratory and the pathologists laboratory from how to decide who to treat, who not to treat, who was going to have a problem down the line. What they found was the stage of cancer, in other words, whether or not the tumor was involved with the prostate alone or outside the capsule or beyond, was very important. The Gleason score, as you know, is what the pathologist tells us. It is number from 2 to 10 telling us how aggressive the cancer looks under the microscope and the pre-treatment PSA level. It is interesting, in Mr. Walsh's original study, a lot of the patients had PSAs over 10, because it was very early and people were getting their first

PSA, walking into offices with PSAs of 10, 15, 20. I remember those days. Now we worry when someone's PSA goes from 2 to 3. In those days, I was seeing people walking in with PSAs of 15 and 20 and fairly advanced prostate cancer in the late 80s.

The other thing they looked at was what predicts metastatic prostate cancer once your PSA starts to go up. Another very important prognostic indicator. The timing of initial PSA elevation after treatment. In other words, if you have surgery, how long does it take for your PSA to start to go up? Or if you have had radiation, how long does it take for it to start to go up? That time period, the gap between a low or 0 PSA to the point where it starts to go up was found to be a very strong prognostic factor in how you do in the future. Again, Gleason score and then a new concept that they looked at was PSA doubling time. How long does it take for your PSA to do from 1 to 2, 2 to 4? In other words, how long does it take to double. By taking all this data and crunching the numbers, they came up with very complicated tables that allowed us to give you some prognosis. Don't focus on that. That makes me dizzy just looking at it. But, what they did was they incorporated all that information and came up with... Dr. Pound was one of the researchers. You heard of the Parton tables. There is a nomogram from Sloan Kettering. So, there are a lot of different researchers looking at this. But, basically they incorporated Gleason score, how many years after treatment for recurrence, the original Pound tables, they divided in greater than two or less than two years. Later they went to three years. Then the PSA doubling time in months. Here they used greater than 10 or less than 10 months. Just for an example, this is your chances at three, five, and seven years of being free of prostate cancer. So, if you are in this group of 5 to 7 PSA, your recurrence happened greater than two years after surgery, and your PSA doubling time was greater than 10 months, at seven years, you still have an 87% chance of not having metastatic disease despite the fact that your PSA is going up. However, if you are in the higher risk group with a faster doubling time, your chances of being free of cancer are reduced to 34%. This was very, very important data at the time and continues to be refined.

We have the same thing for radiation therapy. There is a study showing patients with different PSA cut off points. Notice they are pretty high. This is a PSA less than 9. Then the next line is 9 to 19, greater than 19, and now they include Gleason scores of 2 to 6 and Gleason score of 7 to 10. What this is showing is this is time in years and this is free from metastatic disease. So, if you have a PSA of less than 9 and had radiation therapy, you have an 81% chance at five years of not having a recurrence of that prostate cancer. It falls all the way down to 29% if your

PSA was over 19 and you had a high Gleason score. I believe this was one of the Mass. General studies, Dr. Shiffley, I believe.

So, all this data has come available over the last couple of years to help up decide how to deal with this problem.

How do we treat it? That is what we are here today to talk about today. I am not going to go over this. But, here is a laundry list of what we will be hearing today. Obviously, options after surgery, options after radiation therapy. We are going to be hearing about that. Hopefully...this guy looks a lot calmer than that last guy in facing his demons here. I hope by the end, we will be able to relax a little bit and realize that the fact that we have a problem with rising PSA or recurrence of your prostate cancer that there is still a lot of hope and a lot of options. So, thank you.

**Paul Zatz – Host**

I would like to introduce Dr. Michael Dattoli. His CV is here and I will read it quickly. I am sorry, Dr. Myers. Hold on. It is Dr. Myers. Dr. Myers... As you know he is a medical oncologist, expert in both nutrition and prostate cancer survivor. He has been in front of this group many times. He was a key investigator in creating AZT, Suramin, and phenylacetate while working at the National Institute of Health. He has published over 250 articles and I saw him autographing one of his books for somebody and maybe I could get one also. You can all read the rest of this, because time is short. But, I am very happy to be here, because I have never heard him speak in the flesh. I have seen him on the internet many times. So, Dr. Myers, please.

**Dr. Myers:**

Well, it is certainly great to here for a number of different reasons. The first, of course, is that 10 years ago I came to Dr. Dattoli with metastatic prostate cancer. So, this is my 10<sup>th</sup> year anniversary. My PSA remains undetectable. The second is it is always really nice to visit Sarasota. This is a charming community and from the medical side, of course, it is well-known for the broad strength of its medical community. Every time I come down here, I found out more about what is going on here medically and become more impressed.

They mentioned I am interested in nutrition and that is true, but I am also a medical oncologist who frequently treats advanced prostate cancer. Of course, if you treating advanced prostate cancer, treatments are never as good as you want. That is certainly a moving target. I have a background in basic science, so I am constantly looking at the basic science literature for

insights about how to better manage my patients. This gets to be a formidable task. In 2007, there were more than 5,600 papers published on prostate cancer. This past year, I haven't gotten the final count, but it looks like it is going to be at or about 6,000 papers. Not all of those are clinical. Some of them are in the basic science side. But, I feel that 2007 and 2008 will be looked back on a period of time when we have completely revolutionized our thinking about prostate cancer. I think it is as fundamental as the Copenhagen meeting was for the development of Quantum physics. It is a time when our understanding of prostate cancer and other cancers have taken a very fundamental shift.

In this talk today, I am going to go back and forth between clinical and laboratory observations to show you how this new understanding of the disease transforms how we approach the cancer and help solve some puzzling questions we faced in the past.

So, I am going to talk about...the title is Oligometastatic Disease. "Oligo" means few. This is the concept that just because you have metastatic disease, doesn't mean that you are necessarily in bad shape if there are only few in number. In medical oncology, this idea has great currency for more than 20 years, we have known that if you have colon cancer and it is spread to your liver, we can go in and cut the cancer out of your liver and the chances you will do quite well for years before the cancer comes back. There are certain cancers that can spread to the lung and we can go in and pick the cancer out of your lungs surgically and the patients will go on and do fine for a prolonged period of time. I think this whole concept of the fact that metastatic disease doesn't necessarily mean the death sentence came to its purest expression in a paper in 1995 by Sam Helmon, who was then head of Radiation Therapy at Memorial Sloan-Kettering Cancer Center on Oligometastatic disease. In that paper, he talked about certain broad principles about when a cancer is not likely to be that threatening if it is metastatic and it might be worthwhile getting rid of the lesions. First, there had to be few lesions. Second, and most important, the cancer had to be growing slowly. So, that if you reduce the cancer by 95%, it would take a couple of years for the patient to get back where they were. And third, it had to be a cancer that didn't continue to spread from site to site, hip-hop and skipping across your body. It had to be proceeding in a methodical way. So, this is what I am going to talk about with prostate cancer, the implications it has for treatment.

Now, I am here under the auspices of the Foundation for Cancer Research and Education. The other hat I wear is at the American Institute for Disease of the Prostate, where we treat patients.

These are some of the facts about prostate cancer that were very puzzling in newly diagnosed patients, who were otherwise thought to be excellent candidates for curative surgery. You can find prostate cancer cells in their blood and bone marrow. If you stain for PSA or prostatic acid phosphatase, you can find cancer cells in the bone marrow of half the patients who are judged to be good candidates for surgery. Striking. You would think, well, gee, why go ahead with the surgery? Well, the fact is that there is only a borderline association between finding PSA positive cancer cells in your bone marrow and recurrence. It is as though those cancer cells, by in large, are incapable of doing anything. It is a puzzle. This actually will come up, this fundamental fact, is going to be important in Dr. Barzel's talk, because one of the objections I have heard patients make is I don't want to have a lot of biopsies. It will spread my cancer. They point to papers that show a flood of PSA positive cells in the blood and bone marrow after biopsy procedures. The fact is that we have no evidence that those cancer cells are capable of causing metastatic spread.

Now, Paul Lang at the University of Seattle in Washington has been, I think, one of the leaders in this field and has measured prostate cancer cells in the bone marrow of patients, gone ahead and done surgery, and then followed them for relapse and every year or so go on and check their bone marrow for the presence of cancer cells. A majority of the people who had cancer cells in their bone marrow, the cancer cells disappeared gradually over the first year or two. It was only the patients who at year five, who still had PSA producing cancer cells in the bone marrow who were at really high risk for subsequent relapse. So, this further confirms that those cancer cells are dead-end. They just aren't capable of doing anything.

So, the question is what is going on here? What is the difference between the prostate cancer cells that create metastatic disease and those that don't. Well, this is the heart of my talk and probably the most important piece of science done on prostate cancer in my career. This is a complex slide, so I am going to walk you through it slowly. Is there a...Do I have a pointer? OK, great. This is a Viagra pen. I am sure it will be up to the task. The way we are going to follow this is you have to focus just on the things I am going to talk about and we will move you through. You see a line of cells here. Well, the key experiment here is that...this is all about stem

cells...prostate stem cells, prostate cancer stem cells. Now, we are able to isolate stem cells from normal prostate and prostate tissue. What we see is these are the stem cells and they are rare in number in both the cancer and the normal tissue, less than one-hundredth of a percent of all the population. These give rise to a series of cells that don't make PSA, but undergo steady changes maturing towards prostate...normal prostate cells.

These cells are very rapidly growing. Here you have a graph of proliferation, rate of growth. The stem cells are rare and grow slowly, but they give rise to daughter cells that are capable of very rapid growth as they through this differentiation process. Then finally, they give rise to PSA positive cells that make the testosterone receptor. Now, in the normal prostate and in newly diagnosed prostate cancer, this is 95% of the total population. But, if you look at these cells under the microscope, you can't see any evidence they are growing. We have animals, mice, that have no immune system. They can take human tissues as a transplant and the human tissue will survive. If you take these PSA positive cells that make the testosterone receptor and transfer them into these mice, they don't grow. So, they are not growing in the patient. They are not growing in the mouse. Under the microscope, there is no evidence that they are proliferating. So, the irony is that PSA producing cells that cause PSA anxiety, are dead-end cells incapable of growing or spreading. This is why measuring PSA positive cells in the blood stream and bone marrow in patients is meaningless. You are measuring dead-end cells that are incapable of doing anything.

These cells are the serious problem. This is where the rapid proliferation goes on. Now, how dramatic is this? In Nature and Medicine, they reported a paper where they took normal prostate stem cells, one stem cell and put in the flank of a mouse and it give rise to a normal functioning prostate. Just one cell that looks nothing like a prostate cell. It is a stem cell. It is hard to tell from a bone marrow stem cell, a gut stem cell. It has all the information needed to create a normal gland. If, on the other hand, you took a Gleason 8 cancer out of the patient and isolated their cancerous stem cells and put it in the mouse, you create a tumor in that mouse that looks identical to the Gleason 8 in the patient. So, this is the breakthrough concept: prostate cancer is a disease of the prostate stem cell. Much of what we have been doing focused on PSA has been looking at a bystander. We are targeting the wrong thing.

So, if you come to my clinic and I put you on Lupron and Casodex, these are the cells that depend on testosterone and your cancer shrinks down to this population, which is PSA

negative. So, it is common to see someone, say with a liver mass or large lymph nodes, for the cancer to shrink by 90% on hormonal therapy.

You still left with some abnormality that is PSA negative. You stop hormonal therapy and this rapidly growing population can reestablish this population unless you are able to find some way to stop these cells from giving rise to progeny.

It is very important...these rapidly growing cells are an important target and now that they can be isolated, they can be studied about what is going to affect them and what is not. One of the real shocks is these cells, the more primitive of them, make this protein: ABCG2, which is a fancy name for a drug resistance protein first found in breast cancer. This is the protein that makes it hard to cure breast cancer. Well, low and behold, in prostate cancer that same cell is present in these PSA negative rapidly growing cell and makes them completely resistant to Taxotere chemotherapy. The only difference between hormonal therapy and Taxotere is this population here, which is sensitive. This is the only added benefit of adding Taxotere to chemotherapy tools. Both hormonal therapy and chemotherapy have a difficulty in...because they cannot eliminate the last part of the tumor population. It is a fundamental limit. So, the only way, systemically, therapy will ever gain control of this disease is with one of two things, we either find a way to kill a stem cell selectively and prevent it from giving rise to progeny or we do something about these rapidly proliferating cells.

I think that is all I want to say about this slide...well, this other protein...this protein is an adhesion protein. It is on the surface of the cells and it is key for ability of the cancer cells to attack the bone. It is how it attaches to the bone. This is a self-surface receptor found in stem cells that allow them to continue to proliferate when other cells can't.

So, why do the marrow positive patients remain disease-free? PSA positive cells are not capable of forming metastasis. Stem cell spread must be much slower and more limited, because we have all these people with PSA positive cells in their bone marrow, but no metastasis. Therefore, the stem cells must not be getting there. Understanding the limits of prostate cancer spread and growth is going to be critical for us to understand how to treat this disease.

So, the growth and spread of prostate cancer is fueled by PSA-negative cells. Hormonal therapy and chemotherapy have no impact on the cancer stem cells and on the rapidly expanding PSA-negative population. Success requires that we arrest or kill those.

Here are some key concepts. We just heard about risk of relapse from Dr. Treiman. I would like to go back through them again. They have defined a group of patients who are at high-risk to recur. These people have five-year disease control of 20% to 40% after surgery and by 10 years, most of them are in trouble.

What are the characteristics of this? Extracapsular spread, that is the cancer has penetrated the capsule, a Gleason 8, 9, or 10, and a PSA greater than 20. This defines high-risk patients. Well, I think the first clinical study that made me sit up and take notice was SWOG 87-94. This is a trial that should not have worked based on our previous understanding of the disease. There was a clinical trial that focused my mind on certainly on reading the stem cell literature. On this trial, high-risk patients were subject to surgery and half of them were given radiation therapy to their pelvis. This was done before the modern era of radiation therapy and so the total dose of radiation to the cancer in the pelvis was less than 4000 cGy. This is a dose that everyone would regard as inadequate if you were treating cancer in the prostate. This trial was asking whether a radiation dose that would be completely ineffective against prostate cancer in the prostate could treat metastatic disease, which should be nastier. I remember when the trial was designed, I scratched my head and said what are they thinking. Are they enemies of radiation therapy? But, it turns out the results were rather spectacular. If, after surgery, your PSA was 0.2 or less, 77% were free of disease at five years. If radiation was saved until you fail, only 38% were free. So, here we have this thing of high risk patients, they are eventually going to get metastatic disease, the disease is going to be everywhere, and they are going to die. A low-dose of radiation to the contents of their pelvis outside the prostate was able to dramatically lower their risk of metastatic spread. So, this has a number of implications. The first being, these high-risk patients at the time of surgery, while they were destined to get distant metastatic disease, the cancer cells that were going to kill them were still in the pelvis. This isn't the disease that had gone from the prostate to everywhere. It doesn't go explosively. High-risk patients, this worse-possible group of patients and a screened group of individuals is still methodical and limited in its spread. That in itself was a mind-blowing discovery for medical oncologists, who always assumed that if it wasn't local, it was everywhere. The other striking thing is the cancer cells in this place, where ever they are hiding in the pelvis, are exquisitely sensitive to radiation. Now, you can be excited about the clinical outcome because in a group of patients that are screened, these are the worse cases you see. You don't see distant metastatic disease in people that are

screened every year. We are saying that even in the patients who have metastatic spread, it is still very limited and easy to treat with modern technology.

Years ago, Dr. Dattoli basically addressed the same question and gives us long-term follow-up. In the 1990s, he began to radiate the pelvic lymph node in patients, back when he was up in Tampa. He has published a 14-year follow-up on the radiation to the prostate gland and to the pelvic lymph nodes in this group of patients. You see the high-risk patients, basically no one has recurred after the 6<sup>th</sup> year. It looks like a high proportion of the patients who come in with high-risk disease and who have maybe a 25% chance of being free at 10 years after surgery alone, a sizable proportion of those people can be cured by radiation therapy that treats the lymph nodes in the pelvis. Again, this emphasizes that what is going on here is the stem cells that are capable of creating metastatic disease from the prostate don't go from the prostate gland to everywhere, they proceed in a very methodical way. First, to the pelvic lymph nodes and there elsewhere, in most patients.

There is a subset of people where the disease is much more aggressive. But, this \_\_\_\_\_ now a very large and important subset of patients. So, then the question is, where in the pelvis are these cancer cells. For years, it has been standard for surgeons to do a lymph node sampling in the iliac fossa. Of course, the literature on the success of that lymph node sampling in predicting relapse is controversial and not as successful as we would like. So, recently, there are two studies, both out of Germany, that tried to look in greater detail about where the cancer is in the pelvis. One is a surgical series that methodically dissected various lymph node groups. The other used a technique called sentinel lymph node technique. Sentinel techniques are widely used in breast cancer, where you inject a radioactive isotope or marker into the breast and watch where the isotope goes. If you go where the isotope goes, you will find cancer. So, in this case, they inject the radioactive material in the prostate and then take a picture about where the cancer is spread. Both of these techniques give the same general picture. This is the prostate. This is the bladder. This is the colon. These are the various lymph node groups involved. This is the bifurcation of the aorta, so this is the bottom of the abdominal cavity. This is where the arteries and veins split to go to each leg. This is the vertebral column. You see, the sites that are usually sampled contain some, but not all of the lymph nodes. It turns out that many of these lymph node groups are susceptible to radiation therapy using modern techniques.

The implications are that even in high-risk patients, the cancer is not wide-spread, but is in the pelvis and still in the lymph nodes that drain the prostate gland. The real shock, the unexpected event is that the cancer is very sensitive to radiation at doses that can be delivered. Why is this such a shock? Stem cells are in your body to act as your reserve in the case of a catastrophic event that will kill normal cells. The stem cells are there to repair. So, if you were in a nuclear attack and got a radiation exposure from the nuclear attack that was close to lethal. You would only survive if your bone marrow stem cells were able to survive. Suppose you have a catastrophic illness that damages your GI tract or the stem cells in your GI tract. Well, turn on and replenish your GI tract. You can see this graphically in your own skin. If you burn your skin, the top blisters up and sluffs off, but the skin heals itself because the skin stem cells there have managed to survive and they go through this rapid proliferative phase. Probably the most dramatic example is the human liver. I could go in and cut two-thirds of your liver out and throw it in the garbage can. Two months later we would come back and your liver would be normal size and shape.

How many of you have gone out and exercised and felt like hell two days later. Well, that exercise has seriously damaged and even killed many muscle cells and you can measure the breakdown of muscle proteins in your blood, but the stellate cells, the muscle stem cells get turned out by this and they overdo and you come back stronger than you were before. So, the whole training effect is the same “turn on the stem cells, they rapidly proliferate.” Across the board, the human stem cells are very radiation resistant. It appears that prostate cancer stem cells are unusual in the fact that they are so sensitive to radiation.

We are talking about lymph node metastasis. What about bone metastasis? Among the men who present with bone metastasis, there is a great variation in the speed of progression. Some men rapidly develop multiple bone lesions, but some live for years with the same bone metastasis they start with. I remember one 83-year-old patient I saw, who had a large metastasis to his sacrum, the bone back here in your hip, about this big when he was diagnosed. He was placed on hormonal therapy and eight years later, he was failing hormonal therapy. We restaged him, the cancer is still just in the one spot. There have been no new metastasis form. Well, already you can see that some of these patients are already exhibiting the characteristics that Sam Helmen talked about in 1995. For oligo metastatic disease, where getting rid of the metastasis can have an impact on survival.

The first paper, and Dr. Dattoli introduced me to this, but the first paper in prostate cancer to very explicitly address this question was published in the Radiation Therapy Journal in 2004. This paper came out of the University of Rochester in northern New York State. Ed Messing was the urologist on the study and Bill Herinick was the radiation therapist. Surgeons and radiation therapists got together and they analyzed hundreds of patients that they had seen. You can see the numbers here of the various groups. They looked at several groups. People who had a PSA-only relapse. The PSA was up, but no metastatic lesions. Everyone together. Those with five or fewer lesions. And those with more than five metastatic sites. People with more than five metastatic sites didn't do very well and this is with old therapy. The systemic management was not up-to-date. But, the striking thing is the people with PSA-only relapse and people with fewer than five bone metastasis did roughly the same. Let that sink in. Despite the presence of four metastatic lesions, including bone, those people did no worse than the people with PSA-only recurrence.

In this paper, they approached the issue...now modern radiation therapy has things like stereotactic radiation, where the radiation beam can be focused intensely on small spots, and they proposed that using Sam Helmon's concept, that these patients, these metastatic patients might best be managed by focusing radiation therapy on those lesions. What separates biologically the people with more than five lesions than the ones with fewer. We now know it is the biology of their stem cell. We can now isolate those stem cells and find out what is the difference between these two and we can find drugs to hopefully convert these patients into these patients.

Characteristics of favorable metastatic disease. PSA doubling time slower than six months. Preferably even a PSA doubling slower than nine months. The slower the PSA doubling time the better. Five or fewer metastatic lesions, bone and lymph node. And preferable a long time passing without new lesions developing.

So, this is one reason I would argue for urologists, who are following PSA only recurrences, to repeatedly restage the patients with bone scans and CT scans so if they do develop metastatic lesions, we can know the pace with which they are progressing.

There are other favorable signs. You would like to have effective systemic therapy to give at the same time. For example, if you have a metastatic lesion that is this big, the center of it doesn't have much blood flow and not much oxygen and therefore it is not going to be very sensitive to radiation. If you have effect hormonal therapy or chemotherapy and you can shrink

that lesion, now the remaining cells have a good supply, have a high oxygen level, and therefore would be more sensitive to radiation. Effective systemic therapy makes an easier job for the radiation therapist.

If the PSA doubling time is too high, you have to ask can you slow it down. Because PSA doubling times are so easy to measure and it is still publish or perish in academia, young investigators are constantly publishing papers on things that can slow the growth of prostate cancer down. I have a growing list as a medical oncologist of tools I can use to slow the PSA doubling time down that range for extremely benign to agents with serious side effects. So, you can judge how aggressive you need to be.

There are special cases. Prostate cancers aren't all the same. So, there is an unusual form of prostate cancer that I see where the patient comes in newly diagnosed with PSA in the 1000s. No bone metastasis and the only thing the patient has is limited lymph node disease. Those patients are exceptionally sensitive to hormonal therapy. They will routinely go into complete remission on Lupron and Casodex. But they appear to be very radiation sensitive. I will give you two cases. One is a patient from Long Island, who had a first PSA of 3,600 and presented in renal failure with lymph nodes in his pelvis that shut off the kidney function. His physicians told him that they would help him die with dignity. They projected a life span of less than 18 months. I have seen him in my clinic now close to 10 years later and his PSA is still under 10 and he hasn't failed hormonal therapy. Another patient is from San Antonio, Texas. His first PSA at age 53 was 3,600, a week later it was 4,300. Again lymph node disease only the retroperitoneum and pelvis. Six months into hormonal therapy, a PSA of less than 0.01. At 10 months, no evidence of disease. At one year, we stopped hormonal therapy. Two years later, he starts to recur off hormonal therapy. We restage him using the Combidex scan that Dr. Dattoli will talk about and he has disease limited to his prostate and lymph nodes in his pelvis that are radiatable. I believe he is now in Dattoli's clinic for treatment. There are a subset of people widely metastatic disease, where they can be managed in this fashion.

Determining the extent of disease then is critical here. If you have metastatic disease, we need to really be obsessive about identifying where the disease is. We have a number of different tools. Bone scans are widely used. We all recognize their relatively insensitive. It takes a lot of cancer in one place to make the bone scan positive. There are false positives in that if you have injured your bone it will be positive. The MRI is a big improvement from that. The MRI can spot

a lesion in the bone marrow that is not yet big enough to effect to bone itself. It is much more sensitive. It is much less ambiguous. There is no question to tell cancer from injury. The latest improvement on this is these sodium fluoride bone scan and that is available here in town. For a lymph node disease, we used to have the ProstaScint scan, which had a high false positive and false negative rate. The Combidex scan is a huge improvement. It can spot cancer at a 2 mm size in the lymph node and Dr. Dattoli has some beautiful pictures he will show you using that technique. I think the most serious limitation in this approach to the cancer is we need to improve our imaging techniques.

What about attacking stem cells? Your survival is dictated by the biology of your stem cell. The most promising future direction is to enforce the dormancy of these stem cells...to put them asleep. This is a fundamental property of cancers. Women who have a radical mastectomy can remain disease-free for 20 years and then the cancer can come back. A man can have a radical prostatectomy and have a negative PSA for 20 years and the PSA can start up. Where have these cancers been for 20 years? What we now know is the stem cells have spread, but for some reason, they remain dormant. This has been an area of intense research.

What enforces tumor dormancy? There was one of these absolutely landmark papers published in the Nature Reviews that reviewed all the literature of what we know about how to force the cancer cells into dormancy. What holds them in dormancy after surgery and what can we do to put them back in? There are three things. You can block tumor blood flow with anti-androgenesis agents. You can trigger an immune response against the cancer. The more complicated to explain is what we call tumor differentiation agents. In lay terms, this would be the equivalent of taking a Gleason 10 and turning it into a Gleason 5. These are agents that go into the cell and reduce the machinery of grow and spread. This is a new wrinkle for prostate cancer treatment. It is widely used in the treatment of leukemias and skin cancers. The retinoids do this for a number of different leukemias.

We have a group of agents in advised testing that effectively do the same thing for prostate cancer. For anti-androgenesis, we have Avodart, which is weak, Celebrex, which is intermediate, and drugs like Sutent, which are very powerful anti-androgenesis agents.

To trigger an immune response against prostate cancer, we only today have Lupron. Either alone or given with Ketoconazole or Revlimid, because the prostate cancer vaccines have as yet been quite disappointing.

We also would like to target the rapidly expanding PSA-negative population. It is my own personal opinion that any paper that reports an elongation of the PSA doubling time, has to be effecting this rapidly proliferating pool, because that is what the PSA doubling time looks like.

This is the concept about tumor dormancy from this review. Normal history of cancer. You do surgery and the cancer can stay dormant for months, years, or decades. But, for the section of the time, I am just collapsing that into a few comments. So, with PSA screening, a vast majority of newly diagnosed patients are limited to the pelvis and potentially curable with radiation therapy alone or radiation therapy combined with surgery or other local means.

Many patients with bone metastasis have limited metastasis and can be placed in the durable complete remission with radiation and effective systemic treatment. Thank you.

**Paul Zatz – Host**

Now it is time for Dr. Dattoli. I think he is very well known in the community and around the country. He trained...it looks like he is a New Yorker. I didn't realize that. He trained at Mt. Sinai, as well as Westchester County Medical Center, NYU for Radiation Therapy and a fellow at Memorial Sloan-Kettering Cancer Center. So, we all kind of share a lot of the same pedigree. So, without further ado, Dr. Dattoli.

**Dr. Dattoli –**

Thank you all for coming. I will be giving a sizeable talk here, and many of you have been to my talks and they often are. So, it is good that they have printed it out.

Who is at risk for prostate cancer? There are pretreatment categories and you may not know where you fall: low-risk, intermediate, or high-risk, just to say the higher you go, the higher your potential risk for failing the disease with the highest risk being those having clinical T3a, 8-10 Gleason scores and a PSA greater than 20.

Should you be concerned? Well, perhaps since 30,000 men per year will develop a biochemical recurrence following prostatectomy and another 13,500 patients will develop recurrence annually following primary radiation, which brings us up to that 50,000 number, approximately, that Dr. Treiman alluded to. There is nearly 3 million men currently today living or having been treated for prostate cancer and that number continues to grow.

Most importantly, in a patient who has had treatment and who fails locally, documented local failure, 66 to 75% of men will develop bone metastasis within 10 years and that obviously a concerning point.

What about watchful waiting? Well, I am not going to get deeply into this, but there have been some studies and there is actually been some traction along the lines of doing watchful waiting in men for prostate cancer newly diagnosed. However, if you go back and look at the studies that we all look to, namely those by Johansson and Dolfson, and Sweden and the Danish studies, what you will find is at the end point of those studies was prostate cancer death. There is an inherent problem with that because they either treated with surgery or they didn't treat. The men who they didn't treat and who developed alarmingly high PSAs, who developed bone metastasis, who developed a progression in the prostate region and obstructive ureters, they were put on hormones for every more. Those patients were treated with hormones forever more, so it was a treatment. So, it wasn't truly, strictly watchful waiting. Now, if you look at that data, you will find that more men died in the watchful waiting group. However, when they checked the box at the end of the study, they didn't die from prostate cancer. They died from heart attacks, strokes, broken hips. Well, guess what, what do hormones do in the long-term. We like to use hormones intermittently, but if you use them forever more, they are going to give you hardening of the arteries with hyperlipidemia, they are going to accelerate your diabetes, they are going to weaken your bones. And so what happens is many men will die from the side effects of hormonal therapy over the long term, but in these particular studies from Sweden and Denmark, they did not sensor out those patients were in fact treated. That is why I say they are inherently flawed.

Meanwhile, in the United States, they did do a little better more recently. This was a Medicare/Sear study almost 50,000 patients treated with radiation or surgery and did watchful waiting. They found a statistically significant advantage in men who were treated with radiation or surgery and in fact, the group that benefited the most was the group who were over 70 years of age or greater. Meanwhile, a Lancet study as of May of 2008 found that here in the United States, we are enjoying a greater than 4 fold increase in survival compared to the UK, a country where they do not treat and primarily watchful wait. Again, that is mostly sustained in the older population. It kind of flies in the face of the watchful waiting and the older data. Again, while that is gaining traction, watchful waiting, beware.

Also, if you look at the recent life expectancies, they are getting longer and longer and longer. This is for men. Women you can add a couple of years on to that. Basically, a 70-year-old is going to have over 10 years and even an 85-year-old is going to have nearly five years. These numbers are growing. It is something to be concerned about if, for example, you are an 80-year-old and you have a Gleason 9 tumor, you have a fair life expectancy.

Let's talk about advanced technologies. First, if you have prostate cancer and you have been treated, we got to pick it up. This is just a schematic of your pelvis with the vesicles and lymph nodes. There are tests, which will specifically enumerate cancers, which have gone afar, either in lymph nodes around the prostate or distantly. Combidex and Cinereum, same MRI. It awaits FDA approval, so unfortunately we can't offer it in this country, but it has done very well in the Netherlands and many of our patients do travel to the Netherlands to have this done. The F18FDG fluoride PET/CT we do have available here in the states and specifically in Sarasota where they have done more than any place in the country. The C11 Coline PET/CT which was done at Duke, but again we are waiting for its FDA approval. When we are looking for prostate cancer in the prostate we think in terms of multimodality ultrasound imaging with either gray scale or colorflow Doppler and I particularly like the colorflow Doppler methods. I really have gotten involved with the dynamic or functional contrast enhanced MRI. I think it is superior to any MRI available out there, including the spectroscopic MRI. The Combidex was first published in the New England Journal of Medicine and this was a study in 1993, so it is five years old. I worked closely with Dr. Barence in the Netherlands, since again it is not being done on our soil. What it is showing you here is there are a couple of lymph nodes involved, which were just not detected in any of our tests here. This is a Combidex study and in red, these are lymph nodes. There are a few down here as well. This is important because you would just never had known this amount of lymphadenopathy above the pelvic area in this particular patient.

With the initial Combidex study, 33 of 33 men were identified to have prostate lymph node metastasis following a lymph node dissection or sampling. So, it was 100% predictive accuracy. That has since been further analyzed and the predictive accuracy is up to the 95 to 96% range. Very high. We generally would say the patient has that high a prediction then he should not be subjected to lymph node dissection. Because lymph node dissection does carry with it some morbidities and you may even miss the lymph nodes that you are trying to get and get a false sense that you do not have prostate cancer in the lymph nodes to begin with. Again, this

study does demonstrate that Combindex is enormous in its ability to pick up lymph nodes outside of the prostate, in the pelvis, and in the abdomen. This is another test, the F18FG fluoride PET/CT, which I don't have the slide, but it demonstrates a 89% predictive accuracy. As you see, here is a spot right here, which was not picked up on bone scan in the axial, here it is. Again this is a patient with a tumor in the cervical spine. Interestingly, many men who have positivity on the F18FG fluoride PET/CT, the FDG will also pick up lymphadenopathy, not as well as the Combindex, but it is pretty good. I don't know if you can see it, but there are lymph nodes here in the pelvis, which were not identified on any recurrent studies. Again, here is a lymph node identified in the iliac region on axial. Here is even a lymph node in the supraclavicular region in the neck. We are finding that with more experience, and these were from the Sarasota group, they were getting pretty good. For those patients who can't go to the Netherlands, this might be their next best stop if they happen to have a high-grade tumor, Gleason 8 through 10.

What about the dynamic contrast enhanced MRI? This is neat study. It looks specifically for permeability and we have come to find that cancer is a very permeable to this contrast medium. What this is basically showing you is what standard MRI would show. This is the dynamic MRI and this is a \_\_\_\_\_ out. This is after you remove the prostate and showing the similarities of spots we are showing. What it does is it demonstrates both vesicle permeability, which increases with cancer, and it also demonstrates increased cellular density, which is obviously a pathonomic for cancer. This is just an algorithm showing you how they get there with the high cellular density being more permeable.

Here is a standard T2a MRI and here is the dynamic contrast enhanced. You can see...and start paying attention to how edgy and how to decide prostate cancer does become. This is a study which basically demonstrated...this was a multi-institutional study from Harvard and Austria and Israel demonstrating that with a dynamic contrast enhanced MRI, there was upwards of 75% accuracy when showing that study and the patients going to surgery and then doing the hold mount, meaning having the prostate in the pathologist's hand and seeing where the cancers were. This is again showing just that where the cancer was being shown here and here is a hold mount showing it here. So, very accurate test. I like it. It is also nice to see it, because it is just glaring. It is red. It is just the colors they make it. This is showing you neurovascular bundle involvement on the left side. This patient would not be a good candidate for surgery.

Another positive feature with this study is we have always wanted a study that could potentially differentiate cancers at an earlier point in time, whether they be real or not, because after, for example, radiation \_\_\_\_\_, it often takes years to determine whether a cancer has gone away or not. With spectroscopic MRI, they are 18 months maybe a year. With other tests it could be even longer. But, with the dynamic contrast enhanced MRI we are seeing that we could actually make conclusive statements sooner. This is a patient who was only on three months of hormones. This was the tumor initially and this was the tumor three months later. This was a patient who has had a previous prostatectomy, so his prostate was removed, but here are some areas of cancer regrowth within the prostate bed, which is very important. It gives us ideas of where to zero in on and specifically with newer versions of radiation how you can intensify doses to select areas.

What about Color-flow Doppler ultrasound? This is interesting. This is a tumor in a patient who had previously undergone external beam radiation. This is what you would see if you measured the velocity of that tumor because normal tissues or vesicles don't do this. They pulse with your blood stream. Cancers do this. They don't pulse. They are stagnant. They are there. They may be active, but they are not going in sync with your normal circulating system. They are doing their own thing. This is just showing you at the base in a sagittal image the cancer, which is at high volume. Again, if you just keep focusing on where cancers begin, right along the edge. Colorflow and the dynamic contrast enhanced MRIs are somewhat similar. Colorflow has a pattern of vascularity, which is different. Contrasted to the dynamic contrast enhanced MRI, which more or less as the permeability factor. They are showing you a similar thing in a different way. This is a very dominant lesion in a patient, a T3 lesion. With grayscale, you are just seeing hues of gray or black and white. This is a patient who had previously undergone seeding, and I specifically say elsewhere. The base of the gland is here, but we picked this area up and that did prove to be prostate cancer with positive biopsies.

This is a patient who...I commonly follow patients who have had prostate brachytherapy and we may see something like this which is generalized inflammation, which is no big deal. Those are small capillaries. They are expected to be there. The gland has capillaries going through it. This is a perfect picture. You have the periurethral area and that is the area where you would expect to have some blood flow, while around the area in the peripheral zone you really don't see any colorflow Doppler. These are actually internal hemorrhoids.

This patient here is having a little more urinary symptoms, because the periurethral area is a little hotter. He has more colorflow there, just letting us know that there is some action going on in that area.

Again, this is showing what a normal vessel in the prostate might look like with a bounding pulse. That would look the same as if you were to do a carotid ultrasonography. This is a patient here who has an obvious left base lesion, status post external beam radiation. Again, a very dominant lesion, which may or may not have been pick up by grayscale, but it is distorting the capsule greatly. A patient here is showing the entire posterior peripheral zone being involved by cancer. Again, if you look harder...and then I often say hindsight is 20/20, then you would notice it is darker with grayscale, but it is not so clear until you see it with the Color-flow Doppler ultrasound.

This is a patient again with the nerve bundle involvement on the left side. It is the right side of your screen. You can see where the peripheral \_\_\_\_\_ capsule vessels here across the capsule and communicate with the \_\_\_\_\_ plexus, in this case the neurovascular bundle. So, this patient may not be a good candidate for surgery.

This is a very interesting slide. On the left, this patient is a patient who had brachytherapy and you can see the little seeds and gland. With grayscale, you might just the send the patient home and say there is nothing going on, but look at the Colorflow. This patient had a PSA of 0.1, by the way. I did his biopsies and sure enough, these were Gleason 7, 8, and 9 tumors throughout. PSA can be important, but the Color-flow Doppler ultrasound and follow-up we are finding to be extremely important and will pre-date the rise of the PSA.

With Color-flow Doppler ultrasound, we also look in patients who have had their prostates removed and fortunately this patient has no Colorflow, but what he does have is a prostate remnant, which is 10.79 cubic cm in size. That is a lot. We are seeing more and more of this with laparoscopic and robotic techniques.

Here you are seeing a patient with even seminal vesicles still there. They should be gone after prostatectomy.

A patient here. This is right at the very lower fossa following prostatectomy and it is hot. This patient does have biopsy proven cancer in the prostatic bed.

Again, Color-flow Doppler ultrasound has really brought a very nice tool to the way of following prostate cancers and evaluating for recurrences.

What does the patient do if his Combidx is positive? Here is a patient and his lymph nodes here...He was actually already treated with prostate, which is actually down here and yet these red lymph nodes are identifying disease in the common iliacs and even the preaortic region. He has been injected with a substrate, which is a ultra-small super paramagnetic iron oxide, nanoparticle test and this is what it shows. What you can do is use some very sophisticated radiation techniques and recognize that while I am showing you here the vesicles and the lymph nodes, there is a lot going on around here. There are your kidneys and your bowel and everything else. Here is where you really have to step away from conventional radiations, not 3-D conformal, not IMRT, not IGRT. You have to go beyond that. You have to go into the nano adaptive radiation therapy where you are able to follow the movement of organs. You have to be able to fuse an MRI Combidx with a CT scan to put it in your treatment planning center and then utilize other instruments like the dynamic contrast enhanced MRI or the Color-flow Doppler ultrasound to allow for DART, which in essence, the evolution of IMRT. As I say, IMRT, at least in my clinic, has become obsolete. We have moved on to the point where now we can hit a moving target the size of a dot. We call them voxels, like a pixel on a computer or television screen, but it is space occupying, it is 3-D, so it is a voxel.

My cancer has returned. Find treatment. What to do? Lots of options. I think Dr. Treiman went through some of these...prostatectomy. You can have external beam radiation preferably with more advanced techniques even than IMRT with hormones. You will often here, and again, I know this could become a urology/radiation oncology debate, but patients are often told if they have radiation, they burn their bridges for doing anything else. That is not the case. You can see a patient that has external beam radiation. He still has prostate brachytherapy, cryosurgery, which Dr. Barzel will be talking about. He could have HIFU, biotherapy and prostatectomy by a world-class surgeon. A patient having prostate brachytherapy can have salvage brachytherapy, he could have cryosurgery, HIFU, Biotherapy, prostatectomy. But this group of patients rarely has local failure. It is not so common. Of course there is hormonal therapies, chemotherapy, and going back to the watchful waiting and active surveillance.

What went wrong? A patient had his prostate removed. Why is my PSA rising? I don't even have a prostate. Well, it is all about location. As I was showing you earlier. Cancers begin in the peripheral zone on the edge. They have...the prostate capsule is very, very thin. It just doesn't act as a good barrier for the dispersion of cancer cells outside the prostate capsule. This

is again showing you where cancers begin. It is all about location. Edgy. You rarely find tumors in the central transitional zone of the prostate.

Again, this is with the dynamic contrast enhanced MRI again showing you that edginess, the fact that cancers do begin in the peripheral zone. This is a hull-mount with dyes, which are used status post removal of the prostate, janjun violet or indian ink. It is just showing you that it is a positive margin.

Some history... Dr. Moore back in 1867 said that radical prostatectomy actually violates the principle of surgical oncology. He said that sufficient normal tissue should be removed so that the tumor would not be seen during the cancer operation. It would almost be like saying well, there is a pit in this orange or lemon, so I need to take out the whole orange or lemon meaning you don't see the pit. Weighing in was Dr. Halsad a well-known surgical oncologist at Johns Hopkins said that wide surgical margins are necessary to excise a cancer and that cutting through cancerous tissue may liberate cancer cells and contaminate the normal circulating blood system perhaps beyond the level, which the body can deal with and that was in 1895. He went on to say that if you were to truly do a cancer operation with prostatectomy, you would have to do a total cystoprostatectomy, removal of the neurovascular bundles, and a anorectal resection, also he called pelvic exenteration, leaving the patient with a permanent colostomy, urinary diversion and complete erectile dysfunction and owing to this prostate cancer removal has evolved into a procedure looking to preserve urinary and bowel continence with sexual function, but you really can't live by the codes of cancer surgery with the prostate unless you are willing to remove the bladder, remove the rectum, the urogenital diaphragm inferiorly and the neurovascular bundles. Because of this, Dr. Halsad said by \_\_\_\_\_ of criteria, modern prostatectomy has evolved into a very poor cancer operation and that one would expect to provide a very poor local control. Prostate is way down here and you would have to remove all of that...here is the prostate. You would have to just remove all of that. It is not done. It is not being done. It is not going to be done and that is the problem. For those of you urologists that want to shoot me off the podium here, don't worry, I am going to come down on radiation as well.

What about prostatectomy in contemporary times? This is scary, very scary. Because these are patients who had positive margins and negative margins, but over time, it is a linear fall off. It is shelf. Patient have to ask, I am failing at the same rate on my 5<sup>th</sup> years and I am at the 10<sup>th</sup> year, at the 14<sup>th</sup> years. It just keeps going. So, patients keep failing. If your PSAs are higher

than 10, not doing very well. This would be the perfect world. These are the patients being treated, 100%. If they were cured 100%, the line would go out like this over time. But, unfortunately, it doesn't look that way. So, as the PSAs go up higher, so do these fall offs. What that is basically saying is that patients are falling into a failure mode over time with their PSAs.

These are very recent studies. I am not picking shabby institutions. This is Johns Hopkins, Indiana University, Sloan Kettering, Northwest University. It is just basically showing you that the numbers are less than 50% in patients having radical prostatectomy with PSAs greater than 10. What about Gleasons 8 through 10. Same thing with surgery. Again, Gleasons 8 through 10 picking top institutions, Mayo Clinic, Northwestern, Johns Hopkins. Really bad numbers...27% and the highest you get to is 47%. This is unacceptable.

What about patients with low-risk, intermediate, and high-risk. I first you that slide. These guys are doing OK, but even intermediate is falling off quite substantially and high-risk dramatically. This is very interesting reported at U. Penn by Demico showing you that in a patient who has a positive biopsy with 33-50% core involvement, he is already falling off. If it is 50% involvement, it is less than 50% just in one core.

Perineural invasion appears to be another ominous thing as reported by Johns Hopkins and the Mayo Clinic after surgery. So should you be concerned? Yes.

What about the Da Vinci robot? Does it bring us something better? Not really. At least not by contemporary studies. In 2008 demonstrated that there was a 3x increased failure rate with the Da Vinci robot according to the Journal of Clinical Oncology of Harvard. More recently than that at Duke University, patients who had underwent robotic surgery had significantly higher levels of dissatisfaction and regret than patients undergoing radical retropubic prostatectomy. Well, maybe their expectations were just higher and that is all and maybe these patients didn't have enough experience, that is all. I don't know, but this is what the data is showing.

What to do? Well, there is a real problem after surgery because radiation likes to work in a oxygenated bed. It depends on having those oxygen molecules coming around to create free-radicals to kill the cancer cells. But, in a prostate surgical bed, it is surgically devascularized and denuded and so there is not a lot of oxygen there. Meanwhile, salvage radiation doses are suboptimal. So, what can you do? You can increase the doses substantially using higher ended equipment and you can combine radiation with hormones to exploit that synergistic or super additive effect, meaning  $1 + 1$  equals a bigger number, 3 or 4.

Is this as good as it gets? Well, this was thought to be as good as it gets by Dr. Anchur at Duke and showing that as time went on after a patient who failed from prostatectomy and treated with radiation as salvage that he could perhaps salvage 50% in the long-term.

How do you improve upon that? First of all, we have to determine where is the cancer. Importantly, if a patient's Gleason score was less than 7, no seminal vesicles involved, negative lymph nodes, PSA detectable only after a year after surgery, and a doubling time of greater than six months, he is more likely than not has recurrent disease and you can probably take care of him and cure him. These are studies demonstrating as time goes on the number of PSA \_\_\_\_\_, meaning after your surgery, don't wait too long. As you see the numbers keep getting higher and higher with 74% being by Dr. Solesky at Sloan Kettering. And every in that subset, he found that he can cure upwards, actually 90% or upwards if the PSA was 0.4 to 0.6. Again, the word is, don't wait too long. Don't just sit on your PSA, because when that happens the salvageability of cure is low. Dr. Myers already commended on this. Interesting study, because they looked at immediate versus radiation treated when the patient failed. Interestingly, there was a dramatic improvement in the patients being treated adjuvantly, meaning they were planned to get radiation and not only when the PSAs rose. But, another take home point of this, was a sentinel node IMRT for prostate cancer showed that most of the cancer...lymph node involvement was actually in the true pelvis and in the upper pelvis. And speaks for treatment of the higher pelvic region.

I love this study because what this is showing from UCLA is that patients treated with surgery alone, they are only about 15% cured at over 10 years. This is Gleason score 8 through 10 tumors. But, if they got postoperative radiation to the whole pelvic, look at that, 65%. That is dramatic. So, this was a study at Stanford, again they combined hormones with radiation and found that there is a statistically a significant benefit by doing that in an adjuvant fashion. There is a mountain of studies growing in multi-institutional ways showing that radiation plus hormones is better than one or the other alone.

The conclusion is that PSA matters. Don't let it get too high. Dose matters. You have to treat with a higher dose. Adjuvant is better than salvage. Time to relapse really matters. The grade that you initially had matters. And you must use more sophisticated radiation to decrease the toxicity and exploit the advantage by combining with hormones.

What do you do in contemporary times? Should you be concerned after radiation? How does radiation fair? What about if patients have elevated PSAs. Again, patient perfect graph. The same thing. As the PSAs get high, patients fail. Again, University of Michigan. As PSAs get high, patients fail along with their clinical stage.

What about if they have intermediate to high risk disease? Here is the intermediate. Here is the high risk. So, they are failing. Not quite as high as surgery, but it is there. That is just...I can't even read it. What it is basically saying is, how do you avoid recurrence? In this group, these patients got hormones. They received hormones and they have intermediate to high risk disease. Now we are at least starting to look at higher numbers, 40s, 60s. I mean we are getting up there. There is definitely an improvement in combining radiation with hormones in the contemporary studies out of big institutions.

Again, going with radiation, just stratify by percent of positive biopsies. The patient may say only one out of six biopsies were positive, but in that biopsy, 80% of the core was involved. It is important because if he was there then he is in that red, which means that. He is falling off. He is failing, greatly.

Using IMRT, can we get better? Well, unfavorable, intermediate, unfavorable. So, again the unfavorable and the intermediates are not doing that well. So, should you be concerned after radiation, yes.

What can we do? Well, maybe enhance our radiation ability to beyond IMRT with increasing dose levels, because dose really matters. This is a recent Dutch study and demonstrating a statistically significant advantage with using 78 Gy versus 68 Gy and I would argue, you have to go much higher than that. M.D. Anderson showed the same 78 Gy versus 70 Gy in a statistically significant advantage with PSAs over 10. Again, at Sloan Kettering from 64 to 75 to 81 Gy, they just really jumped up in terms of curing the patients. Using even higher dose levels at Sloan Kettering...this is an eight-year study...they were able to even achieve a 90% with a low risk and 70% with intermediate in the 60s with high risk. Dose definitely matters.

Following definitive radiation there are salvage methods, including radical prostatectomy, which let me just say is about 50%. With brachytherapy, let me just say, it is about 50% properly selected patients. Here is my own data. It is about 50%.

Interestingly though, in salvage brachytherapy after primary radiation failure, up to 98% of the local recurrence may be locally controlled in five-year freedom from relapse is

approximately 50%. And with careful selection, meaning if you don't wait for the PSAs to get up to 10 and you treat them with low numbers, you can start looking at numbers over 80%.

How do brachytherapy-based regimens measure up? That is combining radiation with brachytherapy. So, you are using external radiation and then you are zeroing in with brachytherapy. And I would argue that you can also zero in with more sophisticated types of radiation, IMRT, IGRT. With high grades cancers, again you would love to have this, but you're not. But, you are getting finally some plateaus in the curves. That is important for Gleason 8 through 10 tumors. It is reproducible as you can see.

PSAs greater than 20 are getting plateaus in the curves. This is my own study in Seattle. We have been at it for a long time.

So, how do these patients fair? They are starting to fair pretty well. Intermediate in my study 89% at 16 years, 74% at 16 year for high-risk disease. Again, reproducible. Sixteen years, 80% of the patients with Gleason 8 to 9 tumors are being cured. Sixteen years, I think you have to say cure. Again, it is reproducible. These numbers are...here is an 89% here, there is an 80% here, 60. It is up there. It is not the numbers we were looking at before, 10 to 40s.

This is combined radiation with seeding and again looking at 16 year data for just strictly high-risk disease. I published 74% and with the longest data, 16 years. At 8 years at Mt. Sinai, 83%. These are just generally reproducible studies. You really like to see that. You are not the only one.

Is locally advanced high-risk prostate cancer incurable? Absolutely not. Here it is right here. It is showing you that recent studies are demonstrating that we can get to that, not perfect curve, but we are getting close. These were high-risk patients.

This was the one that is most commonly cited by surgeons Dimico at Brigham. He used MRI to guide his brachytherapy and it was just a failure. But it is the most commonly cited brachytherapy paper.

I am going to leave you with this. This is the first look at our 16 year data at the Dattoli Cancer Center and it has been accepted for ASCO. This is a joint study with the University of Washington in Seattle with 321 consecutive patients treated by one author, myself. These are patients have intermediate to high-risk disease and patients were really held to very strict boundaries in terms of cure, less than 0.2, NADER +2 and ASTRO consensus. Those are the three consensus studies or methods to determine if a patient is free of cancer at length. The

reality of it is, we used all three. We just didn't want anyone to say you didn't do this or you didn't do that. In the patients who did fail, because we didn't cure everyone, they were subjected to saturation biopsies on all failing patients. Not a single one came back positive. The biochemical data was independently re-reviewed and analyzed by the Dr. Walner at the University of Washington, while all the slides were independently re-reviewed by Dr. Larry True at the University of Washington. As you can see, these patients had an average PSA of 20 and a mean PSA of 16.4 and a 52 of the patients had Gleasons of 8 through 10s and most had Gleasons 7 through 10s. Many had clinical stage T3a. So the results are just demonstrating that 89% of the intermediate group are free of cancer at 16 years, 74% having high risk disease with an 86% cancer specific survival. That means prostate cancer... that they survived prostate cancer. They didn't die, as I was saying with the hormonal studies where you can die from heart attack or stroke, but importantly, the absolute risk of failure fell to 1% beyond 5 years after treatment. So, this is the data and it is getting close to that with high risk patients.

PAP ...I have identified numerous times...I have published extensively that it is as important if not more important as the PSA as being a prognosticator for surgery. While hormones conferred no statistical advantage in my patient population here, understand that the patient who did receive hormones had the absolute worst presenting features, meaning PSAs of 50 or 60, Gleason scores of 9. Everything was bad. This is just showing you that over time, patients are free of cancer and they really don't have to worry beyond here, because there is just no further failures at least for now. While the toxicities are extremely acceptable, not a single patient developing rectal ulceration. And as I said, no patient had a pathologically documented local failure who did fail and I mandated saturation biopsies on his prostate.

So, the conclusion is that with these patients having intermediate to high risk disease using strict naders, meaning strict standards of cure, we have done it. And despite the aggressive nature of this study, no local failures have been documented. That is not to say that in the future, others wont be, but very importantly that it is encouraging at five years, we have decreased the failure rate to near 0, or that is what we are seeing. This coupled with numerous other studies do suggest that brachytherapy-based regimens should be considered the standard of care in this group of people.

I love to show this because this is at Sloan Kettering, I actually worked on this in 1989. We found that patients who were properly implanted did well. They didn't develop disease

elsewhere. Back in the day, in the 70s, Dr. Will Whitmore had performed brachytherapy at Sloan Kettering and got a bad rap because they were performing them in an open retropericubic way, not the transperitoneal way. But we came to look at those studies and found that most of the seeds were not even in the prostate. But for those who were, those patients actually did well.

I guess that this would be that based on data, the bottom line for treatment based curability for low-risk group, IMRT equals brachytherapy equals prostatectomy, so you would have to decide which one is best for you. For intermediate-risk group patients, I would say sophisticated radiation techniques, especially with hormones, are at least as effective as prostatectomy, and I will actually say are better. Brachytherapy –based regimens, with supplements or radiation, appears superior to prostatectomy. Basically that is what that says.

This is the references for those of you...I think it is in your handout...who want to check my fact-checking.

New does not necessarily mean better. What I have just shown you is an evolution of what started two decades ago with external beam radiation and brachytherapy. Again, the continuing of pushing the envelope of those two. However, this represents everything that is out there from all kinds of swanky names to newer types of treatments. You will hear about cyber knives. I have mentioned Da Vinci. Soon there will be a Picasso or something else. I don't know. The reality is if you are interested in this chart, we can give it to you and it will describe each one.

### **Host**

Thank you Dr. Dattoli. Just a quick announcement. After Dr. Barzel's talk, we are going to take a quick five minute break and then we will reconvene the panel to answer all your questions. I would like to now introduce Dr. Barzel. Full disclosure...he is my senior partner and probably the reason I have been in Sarasota for 22 years. I actually followed one of my professors, Dr. Whitmore, down here. Actually, the son of the Dr. Whitmore that Dr. Dattoli just mentioned and that is how I found Dr. Barzel. So we have known each other for a long time. Dr. Barzel has been here since, I believe, 1978. He did his original medical training at McGill University and then Fellowship at Memorial Sloan-Kettering where he stayed on and worked under Dr. Will Whitmore. I often wonder why he didn't stay there because he was probably being groomed to be the Chairman there, but luckily he came here and brought his world class expertise along with him. Without further ado, Dr. Barzel.

**Dr. Barzel –**

Thank you very much. Thank you Alan for the introduction. I thank Man-to-Man for inviting me here. You just heard two brilliant presentations by Dr. Myers and Dattoli and I, as a physician, have learned a lot and I am sure you have as well.

My talk today is going to be a little more low-tech. What I decided to do is cover some of the basics. I apologize to some of you who are very sophisticated in prostate cancer and some of this may be redundant. I wanted to go through the basic ideas and concepts and then spend a little bit of time discussing cryosurgery.

The topic today is what to do when prostate cancer recurs after definitive treatment. I am going to focus on the definition, the significance of recurrence, and briefly discuss brachytherapy. I have made these slides myself, so I apologize. They are not the highest technique. What I have here in yellow is the outline of the talk and here on the right is the take-home message. We will refer back to the slide so that we can make sure that we understand how things are going.

The first thing I am going to talk about is briefly discuss curative therapies. Curative therapies or potentially curative therapies, as you all know, are radical prostatectomy, radiation, brachytherapy, cryotherapy, and HIFU. I can tell you that in general, about 25 to 35% of these treatments all fail, unfortunately, no matter which treatment you chose. You can look at studies that show anywhere from less than 5% recurrence to over 50%. To kind of tell you what my practice is..I am basically a surgeon, but I do about 15% of may patients have cryotherapy, about 15% have primary hormone therapy, about 15% go on expectant management, and then the rest are divided between surgery and radiation. I have done all these, except for HIFU. I have been doing it for 30 years. I can, unfortunately, can tell you that every treatment will recur.

The next question I am frequently asked is, Doc, what is the best treatment for prostate cancer? The answer is there is no single, universal best treatment. It is like asking someone what is the best car. You have to know the intended use and for whom. Is it a race car driver? Is this an elderly person going to the store? Is this someone going to school? And where is this car? Is it in New York? The Rockies? In India? So, it is the same thing. When you talk about what the best treatment for prostate cancer, you have to realize that prostate cancer...the impact is a complex interaction between the host..the patient, and the cancer.

So, when you look at the host, you look at the patient's age, life expectancy, comorbidities, psychological makeup, the prostate size, prior surgery, symptoms. These all effect what we do. Then you look at the cancer. You look at the size and stage. The patient could present with a single microfocus of cancer or a very large palpable lesion. You could have a Gleason 5 or a 9. There are other biochemical markers. This is a very complex interaction. Even when you count for one or two or three, it really depends on the whole picture as to what you do. So, there is no base treatment that could be universally applied to everyone. A clinician should not be wedded to a particular technology. There is an old saying, if your only tool is a hammer, you are trying to treat everything like a nail. So, what we do is we individualize therapy on the basis of the patient and cancer characteristics.

We have seen that all treatments fail. There is no best treatment. I want to spend a little time on this definition of recurrence. This is a confusing and I need your full attention here, then you will understand the magnitude of the problem and when I have the take-home message is this is in a state of confusion...almost a mess.

How do we verify successive therapy? In other words, how do you we know that a patient has failed or has a recurrence. We can do physical exams, imaging studies that have been discussed by Dr. Dattoli. What I am going to concentrate on is PSA outcome. This notion is based on inherit assumption that PSA outcome is a surrogate measure of the effectiveness of therapy. In other words, we are going to make the assumption that the way your PSA behaves is a reflection of how the treatment worked. That is not always true because PSA is not the best marker, but it is the only marker we have now.

Let's look at a definition of PSA failure. A gentleman by the name of Cookson looked at literature over four years and he looked at 436 articles. There were 145 articles on radical surgery, 53 different definitions of failure. There were 208 articles on radiation, 99 different definitions of failure. There were 14 articles on HIFU and cryotherapy, 14 different definitions. So, for the total number, 436, there were 166 different definitions. It was like you were following the NFL playoffs and wondered who won and each playoff game was played with a different set of rules. Except here, you have 436 playoffs with 166 different rules. This is why you can take almost any stance in prostate cancer and find a publication that supports your stance. That is why you can't get a straight answer from any of us when you come and say what is it, because we don't know. These things aren't comparable.

Now, we are not doing this to make it difficult for you. The next few slides will show you why we are in this dilemma. It is the interplay between specificity and sensitivity. I am going to give you an example that everyone understands, which is PSA example.

If you are looking for specificity of a test, let's say we are going to wait until the prostate is rock hard. I am old enough to be in the generation where patients presented with a rock hard prostate and if you waited until both lobes were hard, there was about 90% chance you would find cancer. So, here your biopsy would show cancer 90%. Very specific. Or you can say, look, we are going to wait until the PSA is over 30 and I will wait and do biopsies then. Well, you are going to have a very high percentage of cancer. So, that is where you go for specificity.

Sensitivity...when you go for sensitivity, you are really trying to say I don't want to miss any cancers. I want to pick every cancer. So, then you start doing biopsies of any PSA over 1. I dare say that you would pick up most of the cancers, but then you would have 99% of the patients have unnecessary biopsies. So, what happens is that we come with a compromise. Up until a few years ago, we used to use a PSA cutoff of 4 and now we use a PSA cutoff of 2.5. That is a compromise between specificity and sensitivity and if you use that cutoff, about 20% of patients will have cancer. So, it is not a very specific test, but you need...this is the problem we have. How this relates to the problem at hand is that we ask ourselves, should we lean toward sensitivity or specificity. The urologist went for sensitivity. They say any PSA over 0.2 if confirmed after radical surgery means recurrence. Radiation therapists went more for specificity. The ASTRO 1996 had three consecutive rises in the PSA and the Phoenix 205, which is a nadir plus 2, is again a very specific definition. These ASTRO definitions over-estimate biochemical free survival. And they estimated about a five-year delay between detecting biochemical failures after radiation as opposed to surgery. That is not to say that surgery is better, I am just telling you what the status is. There is a lot of reason to go for specificity, because specificity is more clinically relevant than sensitivity.

In any definition of biochemical failure, we have to strike a balance between sensitivity and specificity. When you are going for sensitivity, it helps in determining cure. It is great for articles. When you go for specificity, this correlates more with clinical outcomes. This is why the ASTRO and the Phoenix definition went for specificity. This is why the area is very confusing because everybody uses different definitions, they are looking for different endpoints. It is not

because we are trying to make things confusing, but that is why we can't give you a straight answer sometimes.

So, we have seen that curative therapies...all treatments will risk failure. Treatment options...there is no best treatment. Definition is in a state of confusion until we get a better test than PSA. I think once we get a better test than PSA and better imaging modalities, that confusion will disappear.

What is the meaning of recurrence? I am going to show you just a few examples where when a patient has a recurrent PSA, the appropriate response is "So what?" Not every PSA recurrence is a problem.

When we are trying to determine if a PSA or biochemical failure is significant, we look at the age of the patient. Is the patient 50 when the recurrence occurs? Or 80? How long did it take this to relapse from treatment? Did the patient have a radical prostatectomy 12 years earlier and now has a recurrence? Or did he have a radical prostatectomy a couple of months ago and now has a recurrence? What are the PSA kinetics? How fast is the PSA growing? Dr. Treiman showed you this slide where after surgery when the PSA first recurs, it takes 8 years to metastases and five years from that to death. I have a number of patients in the late 70s, who are 10 years post-radical retropubic prostatectomy have long doubling times. So, I am not too concerned with that patient. Many radical retropubic prostatectomy for some reason have a PSA that stabilizes around 0.5. I offered them radiation and they said no and we just watched them and for years and years, the PSA never went over 0.5. If you take a 79-year-old who is nine years after radiation, he has a rising PSA for five years, presents a 3.2 and his PSA is doubling every 18 months, that patient probably should be watched. So, in these instances, the appropriate response to PSA relapse is "So what"? It is not really going to effect things.

So, in summary, PSA failure may not be a clinically relevant endpoint and should not be relied upon as a sole basis for changing treatment. It is an important tool for standardizing reporting and comparison of results.

Now, we are going to look at salvage options. When the PSA recurs, we are faced, after curative therapy, with a dilemma to try to decide if this is a local recurrence...In other words, did it occur in the prostate or in the prostate bed, or is it due to metastasis...cancer spreading outside the gland. This is, of course, an important determination, because if it spread, then you will need systemic therapy like hormones and if it is still in the prostate, you might have a chance of

salvage treatment. So, local recurrence, we might go for salvage treatment. Distant spread, hormone therapy. And of course, you can have a combination. A patient could have local and distant. Unfortunately, current imaging modalities are usually not sensitive enough. Now, there are some new ones that Dr. Dattoli and Dr. Myers spoke of and I am sure that this will not be the case in a few years, but currently, the imaging modalities are just not sensitive enough.

The analogy I give patients...and permit me a little discretion here, is if you put a dot on a piece of paper, you can probably guess that there are about 10,000 cells in that size of a dot, but most imaging modalities need somewhere between 3 to 5 mm to see the cancer. So, when a patient comes and I tell them that now you have developed metastasis, they say, but doc, you did a bone scan and it was negative. How could that be? Well, when you have a negative bone scan, it is saying you don't have anything this big. But, you could have a lot of these critters in the bone and not see it. That is the problem with imaging modalities.

So, how do we decide if it is local or distant? We rely on time to detectable PSA, how long did it take for the PSA to come back and the doubling time in exact science at best. So, even when we are treating recurrence, we are never sure that the recurrence is local only. So, all these treatments that we are directly locally may not be effective if a patient has distant spread as well.

So, I put this slide to kind of go over what the options are. The primary therapy is in black and it is labeled one and the secondary therapy I put a two. That is the secondary therapy. So, lets say the patient has a radical retropubic prostatectomy or surgery. Well, all these treatments, by the way, could have observation or hormone therapy depending on the dynamics are. So, I didn't put these columns to confuse things. So, if the patient had a radical retropubic prostatectomy, rising PSA, you could certainly offer observation depending on the PSA kinetics or hormone therapy. But, in terms of salvage treatment, well you can't do another surgery. You can't do seeds, there is really nothing there unless it is a botched up radical, which...you can't do cryo. So, the only thing available is radiation therapy. Now, let's say you have external radiation therapy. Well, you could have observation, hormone therapy, radical retropubic prostatectomy I put a small plus, yes it can be done. I certainly have done a number in the years before cryo. It is a very difficult operation and fraught with complications. It is not advisable to give more radiation, obviously, because you usually...you hope the first dose was the tumoricidal, the maximal tolerated dose. It is tricky to do seeds, but you can do them. Some places do them. You have to be very careful on your dosimetry not to over exceed the radiation tolerance. Cryo is a

very good option, in my opinion, for salvage, once you have proven that there is no cancer metastasis. With seeds, again, I have done a few radical retropubic prostatectomy and I don't want to ever do another one after seeds. It is a very exceedingly difficult operation. But, this was in the time where there was no cryo. No other option. You can do remedial brachytherapy. It is a very interesting concept. I have tried to sell it to Dr. Zoleski at Sloan Kettering, by doing a mapping procedure after seeding. And sometimes if the seeding wasn't done quite right, you might find cold spots where the cancer is and then you can do another seed, a remedial seed procedure. Currently, I think that the optimal treatment, in my opinion, if the patient has brachytherapy and he has relapse providing he is in the right category and doesn't have metastatic disease, is cryo. And for cryo, I don't think anyone has every done a radical to my knowledge. Seeds would be difficult because the gland is fibrotic. The options are first radiation and second would be another cryo ablation. So, we discussed...I am going to talk a little about cryosurgery.

Cryo is Greek for cold, therapy is Greek for healing. Cold-healing. That how the term was developed. Basically, it is done under ultrasound guidance. You put these small needles. You pump Ardon gastrostomy through them and the prostate is cooled to (minus)  $-40^{\circ}\text{C}$ . You have a catheter in the urethra that warms the uretra so the uretra doesn't slough. We no longer use this tube in the bladder. This is an old slide. The big thing is there are no major incisions. It destroys cancer cells during the procedure. It is an outpatient procedure and it could be repeated.

Best practice guidelines in 2008 came up with the salvage cryo patient selection. In other words, who is a candidate for salvage cryo. You have to demonstrate that it is organ-confined disease. You have to have a positive biopsy showing that the cancer is still in the prostate. Your PSA should be less than 10. You should have a long doubling time to suggest that it is local rather than distant. You should have a life expectancy over 10 years. No seminal vesicle involvement. And a negative metastatic work-up.

I just wanted to give you a little minute or so to explain to you why I got interested in Cryo. About five or six years ago I got interested in cryo mainly because of this report where they took a 10-year period and looked at all these different treatments and compared results between radical, brachytherapy, external beam, 3-D conformal and what they found is that for the low and moderate there was not a big difference. The thing that struck me is that in the high-risk patients, there was not a fall off with cryo. In the five-year biochemical disease-free survival,

with cryo seemed to stay the same. It did not fall off. I think the reason for that is that when you do cryo, you are freezing a good cm or more outside the gland. So, this a margin independent treatment, if you will. If the cancer is outside the gland and you do surgery, you are going to leave a positive margin, there is no question. I think external radiation is better for margin, but cryo will really...you can get the margin to  $-40^{\circ}\text{C}$  because you can put a thermal couple here and just wait til it registers  $-40^{\circ}\text{C}$  before you stop the treatment. This is obviously a very aggressive treatment, and if you do it on both sides, patient is going to be impotent, because you are really not just getting the prostate, you are getting to all the surrounding tissue, like the Holstead approach that Dattoli talked about where you are really getting the prostate and surrounding... This is how I got intrigued with doing this. In the first 30 patients that I did were all very high-risk patients. Patients that I knew that would fail other treatment. Patients who had a lesion that I could feel on rectal. They had Gleasons 8 and 9 cancers. Very advanced cancers. I was so impressed with the result that I continued to do it. In fact, I love having a patient that is having a cryo seven or eight years ago coming to the office and I will get one of my partners to do a rectal to guess what he had and they think he has had a radical prostatectomy, but he has had a bilateral cryo. So, it is a very aggressive treatment. It is not meant for everybody. Only about 10 to 15% of patients, I think, are candidates.

So, where does it fit. Well, we are discussing salvage therapy, but cryo fits in the very advanced case, in my opinion. And a very, very early case where a patient is considering doing nothing. And as a single microfocus of cancer, I have done a number of what is called lumpectomy where we just go in and freeze a little area of cancer. This is an alternative to doing nothing.

This is the salvage cryo results. Again, this is AUA Best Practice Guidelines. Negative post-salvage biopsy is 93-94%. Biochemical disease-free survival, wide range, lots of complications. Incontinence about 10%. Fistula 0-3%. Sloughing of the urethra. Erectile dysfunction. Because of these complications, I am very reluctant to do bilateral cryo, both sides on patients, as a salvage. What I started doing is focal conforming, or what will be called male lumpectomy. In other words, if the cancer is only here, possibly we could just treat that area and avoid treating the rest of the prostate. This is in the salvage case. We are talking about a patient who has had radiation or seeding and the prostate has already been damaged and we don't want to do more damage and limit complications.

In the future, I think there are going to be some of the new imaging modalities that were discussed are going to show us where the cancer is with certainty. But, what I have done now is sort of a very basic crude method, which is to do a mapping biopsy through a grid to tell me where all the cancer is. I first described the technique back in 2001 and I have been presenting a number of places and lately, people are getting more and more interested. Duke had a first World Congress on Focal Therapy. I was invited to discuss mapping. I was also invited to speak in London.

Basically, it is very simplistic approach. It takes a brachytherapy grid. You superimpose the prostate and you do a stereotactic biopsy. Basically you have XYZ coordinates on all your biopsies, so you know where the tissue is coming from and you plot it out to get a map. This is an actual case. This is the ultrasound machine in the prostate. This is done under strictly sterile conditions. This is the grid and we are doing a map with this biopsy. Then I put it on a placemat, divide the prostate into zones, so there is no confusion with pathology, and then we divide it into 26 zones. Here is a mockup pathology report. This is actually a real pathology report of a patient. This patient had negative transrectal biopsies and with mapping, was found to have extensive cancer in the anterior zone. This is the zone that we can not get to from the rectal. The nice thing is that we can freeze the top half of the prostate, spare the rectum, spare the urethra in the lower hemisphere, and spare the neurovascular bundles. This patient underwent what I call conformal cryoablation. So, focal freeze means putting a couple of probes and just freezing the lesion. That is only done in patients who had a very small cancer proven on mapping who say I don't want to be watched. I want to get some treatment done as an alternative to expectant management.

Conformal freeze is what we are talking about after radiation failure. This really limits the complication almost to nil. Very, very low, 3% incontinence rate and no fistula, because we are not treating the whole prostate. We are preserving part of the urethra and part of the prostate.

This is an example of a focal therapy. This was actually on a patient who was...this was an alternative expectant management. The lesion was here. Put a couple of probes and froze...here is the ice ball. The ultrasound is coming from here, so when it hits the ice ball, it can go through, that is why you see dark past it. What I usually put is some saline between the prostate and rectum to move the rectum away, so that you can freeze aggressively and not worry about getting the rectum. This is what it looks like. This is preoperative. This is postoperative.

You can see we truncated part of the prostate. It is a very aggressive and destructive process, cryo, freezing.

Now, we have discussed and you can see that if you are going to use cryosurgery salvage, it is better off to do a lumpectomy, in my opinion. It gives you, I think, equivalent results with no morbidity. In patients who have already had a procedure on their prostate, you really want to eliminate morbidity. I don't like complications. Stay away from anything that causes them.

I just wanted to give you some salvage choices to show you how we individualize things. We will go through this real quick. Let's say you have a 57-year-old and he is four years following a radical prostatectomy and his PSA has gone from 0.2 to 0.3 to 0.5. Well, this patient, in my opinion, is a candidate for radiation, salvage radiation therapy. That is if his metastatic work-up is negative.

Take the same patient, 57-year-old, now he is nine-months post-radical. His PSA is going up rapidly. It has hit 4. That person has metastatic cancer. He does not have local cancer. It is not likely that radiation is going to help him and he is better off with hormone or systemic. If he is this age, I like to even try chemotherapy.

Now, let's take a 77-year-old. He is nine years post radical retropubic prostatectomy. His PSA is rising slowly. I might put him on diet and lifestyle modification to start off with. I will keep a real close eye on his PSA and if it is rising rapidly, I would probably go to hormone therapy, although if he was a really young 77-year-old and had a five or 10-year life expectancy, I would not deny him radiation.

Now, let's look at a 60-year-old who is four years post-radiation and his PSA has gone from 1 to 1.3 to 1.9. Now, he has not met the criteria established by ASTRO. He has not met the nadir plus 2. But, this is young person. I would consider him for early biopsy. Not wait. Do a salvage, focal cryo because he is 60.

Take the patient and now make him 79. Well, we are not going to do that. We are going to do diet and lifestyle modification and then if the PSA rises rapidly, then go to hormone therapy.

The last patient...he is a 77-year-old. He had radiation six years ago. PSA rises...the doubling time is say over six months...something like 12 months. But, someone has done a biopsy and it is a Gleason 8 or 9. Now, even though he is 77, I would consider him for mapping and focal cryo if he had a good shot at five year life expectancy. So, you can see that the option

really depends on a variety of things that have to do with the host, which is the patient, and the aggressiveness of the cancer.

So, in summary, with salvage choice, tailor treatment to the patient. So, we have seen as a summary, all curative therapies, unfortunately, and I have tried them all, they all risk failure. So, it is hard to choose. The treatment option...there is really no best treatment option that could be universally applied to every patient. The definition of recurrence is in a state of flux only because we don't have a good tumor marker. PSA is not a good tumor marker. We are going to get a lot better ones. And I think this will improve the definition. The meaning of recurrence sometimes it is very significant and you have to act. A lot of times, it is a so what. You really have to consider everything. We discussed salvage options. If we are going to do cryosurgery following radiation, I feel very strongly that we should not be doing the whole gland unless there is cancer everywhere, because the morbidity is too high and I think we should do the lumpectomy or the conformal cryo. And lastly, salvage choice should be tailored to the patient.

**Host –**

We have a lot of questions. We will do our best. It is about 12:00. We will go for half an hour. I will stay behind a bit and if anybody has any burning questions that we don't answer, I will stick behind and try to do my best to answer them.

Alright. The first question...boy I thought my handwriting was bad. Some of these I will not be... alright. This is a very basic question. A lot of these questions will repeat, so I will edit them.

**Q: Can I stop hormone therapy? That is a very basic question. Rising PSA after 10 years. Radical. I am not sure what that means. I think we touched on this. It is a good general question. If you are on hormonal therapy, at what point is it reasonable to stop it? Let's assume that PSA is stable or unmeasurable. I am just going to go down the panel here. Because this is a very basic question that I saw a lot of.**

**A:** Well, of course, you are alluding to intermittent hormonal therapy. I think you mentioned the side effects of hormonal therapy. The problem with continuous hormonal therapy is the cardiovascular risk is very significant. The risk of heart attack, stroke, diabetes. The basic underlying problem is that hormonal therapy makes you insulin resistant, which is the precursor to developing diabetes and it makes your cholesterol patterns go crazy and it causes systolic hypertension. First of all, if you are on hormonal therapy, you need to have some doctor looking

over your cardiovascular health who is very aggressive at treating you, but there is this huge cost of continuous hormonal therapy that hasn't been appreciated until recently. So, I think, unless there is a very powerful reason, everyone should be on intermittent hormonal therapy particularly if you have cardiovascular risk factors because of this. Our usual criteria is that we drive for a PSA less than 0.01 during hormonal therapy. We like to hold that for a number of months before we come off hormonal therapy. Because we find that if we do that, a certain proportion of patients, cancers will stay dormant even though their testosterone recovers. If you come off hormonal therapy and your PSA is 0.5, as soon as your testosterone recovers, your PSA will, too. But, if you get into a true, complete remission with hormonal therapy, a portion of patients will not recur after they come off hormonal therapy, particularly if you are left on Avodart. So a big thing for us who do intermittent hormonal therapy is to find those things that slow the regrowth of the cancer after you come off hormonal therapy. That is how I got into the Mediterranean Heart Healthy Diet, Avodart, Celebrex, vitamin D, the supplements, the same things you would use in watchful waiting tend to slow the regrowth of the cancer. So, that prolongs the time you can stay off hormonal therapy. If you don't do anything and come off hormonal therapy, most men are back within a year. So, if you are on for a year, you are off for a year. In fact, a good rule is the number of months on equal the number of months off. If you do things we are talking about, you might be on hormonal therapy for one year and off for three or four years before you have to go back on. So, God is in the details there.

**Another panel member:** Little to add, but that I am a big proponent of intermittent hormonal therapy and what I usually use is the patient's baseline PSA, meaning what he came in with initially, his pre-treatment PSA as to when to resume his hormones again. Because that becomes a real issue, when do you start again.

**Another panel member:** I am in agreement. Just a couple of things. My approach to hormone therapy has changed as new evidence has come around. When we first started, I had a patient on permanent therapy. Then reports came out that patients might do just as well with intermittent therapy. And more importantly, the troubling thing is that, especially in older patients, even after a very short course of hormone therapy, you can become permanently unicoid. What that means is that if you are on hormone therapy for as little as six months, but usually about two years, that when the hormone therapy is stopped that your pituitary testicular axis does not recover and you stay permanently unicoid. I have a number of patients who have

been on hormone therapy for a long time and you do their LH and testosterone and their testosterone is still unicoid as if they were still on it. So, I do have intermittent therapy. Recently, because of the side effects that Drs. Dattoli and Myers alluded to with cardiovascular and bone, etc., in just the last six months or so, I have started using graded therapy where I might not start on LHRH agonist right off the get-go and may start on Casodex until they fail that. I am not sure if that is the right way to do it, but I am just a little concerned about the insulin insensitivity, cardiovascular, etc.

**Q: I just want to stay on the topic of hormone therapy. There are a lot of questions about the timing of Casodex related to when to start it, when to stop it in relation to hormone therapy. Again, I will just go down the line on that.**

**A:** Casodex is a pure antiandrogen. The first antiandrogen we had was Ulexine or Flutamide. The trick there is that Flutamide wasn't active by itself. I had to be activated in the liver. So, you had to be on Flutamide for a week or two before enough Flutamide was activated by the liver to block testosterone. This is important because when you give Lupron or one of those drugs, testosterone actually surges. It goes up 150%. You had to protect patients from the flare. Casodex comes along and just observing my colleagues, they have a mixed approach. Some people start Casodex with Lupron because it doesn't need to be metabolized. Others will start Casodex a week beforehand. So, I think there is rarely an explicit discussion of this issue with regards to Casodex. So, here are the facts. Casodex does not need to be activated like Flutamide. It works right away, but it accumulates slowly in the body. So, if you take one Casodex a day, the blood levels will continue to increase for the first month. So, full blockade can take a while to take place. So, if you start one Casodex a day, the day of Lupron, there will not be enough in the body to prevent the Lupron flare. I am a pharmacologist and in pharmacology when you have a drug that accumulates slowly over a period of time, the solution is to give a loading dose. You just give a big dose the first day. There are equations where you can calculate that. So, for Casodex, if you give three pills the first day, you will be fully therapeutic within two hours. Medically, as a practitioner, if a guy walks in your office and you have to give the Lupron that day, you can't wait the week, suppose someone has impending cord compression, the cancer is pressing on the spinal cord, something like that, just give three Casodex that day and you can give the Lupron shot and you will block the flare. So, this is just a little bit of these details. Some of us use high-dose Casodex routinely, three Casodex a day,

because when you are using Casodex alone, three Casodex are more active than one, so we feel it give better blockade. If I see a Gleason 9 or 10 and I am trying hormonal therapy, I will do that. If you are going ahead with triple Casodex, there is no problem with the flare. The testosterone is going to be effectively blocked anyway.

**Another panel member:** Again, little to add, but that I treat many people who come from afar, and they may have their flights for the next day and don't know where they are going to get their Lupron or Trelstar injections, so I often give them three Casodex as a bolus and give them their injection right then.

**Q: The next many questions refer to something that I know we are all interested in this and we touched on it briefly. Lifestyle and dietary therapy, very important, and I know you are all interested in that. So, again, I will ask the panel to comment. A lot of questions about, for example, the pros and cons of supplemental calcium, use of Avodart as an intermittent hormonal therapy as well.**

**A:** I think you actually did a nice job of reviewing the fact that not everyone who recurred as got life-threatening disease. The people with slow PSA doubling times. I think there is a growing recognition that if someone has a PSA doubling time of 9 to 12 months, you don't need to come in and put them on aggressive hormonal therapy and make them miserable. There is a subgroup of people who have recurred, who have slow-growing disease, and that the PSA doubling time, the cancer progression can sometimes be slowed dramatically or even stopped by simply going on a heart-healthy diet. It is hard to argue against this... A Mediterranean heart-healthy diet is beneficial for many diseases. It reduces the risk of diabetes and reverses metabolic syndrome. There is a randomized control trial the past year that it doubles the survival of someone with Alzheimer's disease. It dramatically reduces the risk of heart attack. It is sort of a no-brainer to go on a Mediterranean heart-healthy diet and if in the process, it slows the cancer down enough to arrest progression, then that is a reasonable alternative. Avodart with cut the PSA in half within the first month and that is irrelevant and should be ignored. It is PSA doubling time, again, for all these things that count. Diet and lifestyle, I think, definitely have an impact. Now, when it comes to supplements, the ones that seem to be most dramatic to me are vitamin D and the work out of UCLA with pomegranate. I would say that of the unpublished agents, the one I am most excited about is resveratrol, the active ingredient in red wine, which I some patients seem to be quite spectacular.

**Another panel member:** Again, little to add. My only concern with patients having PSA relapse and I showed you those who have had removal of the prostate and their PSAs are at a certain value and they become detectable and then you begin to track them. They may often have had or at pre-treatment had a Gleason 7, 8, 9, or 10 tumor and it may have mutated through the years, sometimes the PSA in and of itself can be a little unreliable and it can fluctuate and even go down when in reality it is cancer that is mutating to become more aggressive. That is why, for example, we don't pick numbers of greater than 10 in patients who have had surgery and then their PSAs have come back. Instead, we pick numbers like 0.2 or between 0.4 to 0.6, because it really gets us alarmed when their PSAs get higher, but more importantly, the data stands very strong that the lower the PSA is that you treat the patient, the higher the probability that you can actually cure the patient.

**Another panel member:** I am a big proponent of diet and lifestyle changes. In fact, when a patient first comes to the office, the first diagnosis of prostate cancer, he is given information in dietary advise. There is circumstantial evident that it helps. There are a few studies that show it helps. Just consider one thing, the incidence of histologic prostate cancer, that means prostate cancer at autopsy, is the same here as in China in some provinces. The same all over the world. The incidences of clinical prostate cancer is 100 time greater in the United States than some provinces in China. It is diet is what is doing it. The only male \_\_\_\_\_ that gets prostate cancer is the domestic dog because he eats our diet. Diet is there. It may be too late by the time you institute it, but I figure there is no harm in trying it. So, everybody should have...go on so-called prostate cancer diet. I also use resveratrol...actually I take it. It is an interesting compound. There was one study actually that showed that if you go on a diet and you do meditation or get into a support group, and they have shown this with prostate and breast, that it decreases the doubling time of PSA and improves the survival with breast cancer. I don't think it is true for all cancers. I think that breast and prostate are very similar. My old chief, Dr. Whitmore, would have slides showing the pathology and nodule distribution that they have similarity and they are both hormonally sensitive. It makes sense that things like meditation and support groups...whatever...that changes your hormonal \_\_\_\_\_, may somehow change the behavior of the cancer. These are all positive things. They may not work, but there is no harm in trying. As Dr. Myers pointed out, all these diets will help your cardiovascular health.

**Q: This is actually a question, interestingly directed to Dr. Dattoli. Understanding that dose matters or more radiation is better for cancer control or sure, can you comment on how to prevent or treat the side effects from radiation?**

**Dr. Dattoli:** Again, the higher technologies that have evolved through the years will lessen the consequences of radiation complications. Having said that, bear in mind that the prostate is entangled between all these critical organs, the bladder, the rectum, things which matter so that you would expect the patient to have some degree of proctitis, some degree or urethritis, perhaps cystitis. We solely treat prostate, so we manage their symptoms the best we can using a variety of regimens ranging from prostatitis protocols or using combined anti-inflammatories, such as Celebrex, which has these antineoplastic effects as well, along with alpha blockers, along with antibiotics for a longer period of time, three to four months. If that fails, we often, and actually encourage our patients following treatment, to go on agents like pentoxifylin, Trental. Since it is a wonderful agent to providing blood flow to areas that otherwise would not get it. We know that healing comes with blood reaching those areas. That works in a sizable number of our patients. Thereafter, hyperbaric oxygen could be thought of, since it is a tried and true sort of therapy for treating complications of radiation sequela.

**Q: Question for Drs. Dattoli and Myers: I just saw a report that can out that statins...patients on statins seem to do better with radiation. Do you think this is a true finding?**

**Dr. Dattoli:** Yeah, I recently saw the article. There is an article coming out every day to suggest something. I don't know the mechanism that may be the case. Again, another agent like Celebrex, which has it's COX-II inhibition and it is potentially anti-\_\_\_\_\_plastic, I often like to have patients on statins because they, too, have been identified to be antineoplastic. I encourage a patient who even has a borderline cholesterol to be on a statin. I don't know. I think the jury would still be out with respect to using statins in that scenario.

**Dr. Myers:** I actually had a personal interest in this. In 1990, there was a paper published from Harvard that the statins could be used in tissue culture to synchronize tumor cells. I remember in 1992, we will setting up to do an experiment where we had to have all the prostate cancer cells growing in sequence, so we put the statin dose that are used in other tumors and we came in the next day and the plate was clean. There weren't any live prostate cancer cells. So, beginning in 1992, I began a clinical trial of treating prostate and brain tumors with

Lovastatin, which was the first statin. We started with the standard dose of 40 mg a day and increased the dose to as high as 4000 mg of Lovastatin a day. We saw only minor activity against prostate cancer at a dose of 4000 mg day. It showed spectacular brain tumor responses. We saw, as a major side effect, muscle pain or weakness. We showed that was due to Q10 deficiency. That was the first paper that showed Q10 would reverse the myopathy. So, I can state with confidence that the statins used at the routine doses have no direct anti-cancer activity. In the test tube, there is a radiation sensitization of the statins, but the clinical data is very mixed. But, again, I keep seeing on the internet, oh, take statins. They have activity against prostate cancer. Statins plus Celebrex is supposed to be magic. I can tell you I have lots of advanced patients with statins on Celebrex and the anti activity by themselves is nothing. I don't know whether there is going to be much with radiation yet.

**Q: There are a lot of questions and I am going to group them together. We didn't really didn't address this on chemotherapy. I guess Dr. Myers can address this. I know that is a lecture in and of itself, but I have a lot of patients who have failed all the other treatment options. We really didn't talk much about chemotherapy today. So, maybe a quickie on that.**

A: Remember the stem cell slide and I showed you what form of the disease hormonal therapy kills and chemotherapy adds an extra piece to this. Neither hormonal therapy nor chemotherapy can get rid of the stem cell, in general. However, if you take a large number of people and put them through hormonal therapy or chemotherapy, there will be the occasional patient who goes into complete remission. This is something that when you are dealing advanced disease to remember that there is always hope that you might be lucky. To give you some specific examples, there was a big clinical trial published in 1989 by David Crawford on hormonal therapy and bone metastatic disease and 15% went into complete remission. That is, the bone scan cleared out. Two-thirds of those people were alive 20 years later. Again, complete remission \_\_\_\_\_. The same thing with chemotherapy. So, often when you are talking among oncologists or you look on the internet, people trump at the fact that Taxotere prolongs life four to six months, which is what the trials show, but 50% of the patients without chemotherapy are dead six months earlier than those who had chemotherapy. That misses a key point. There are a subgroup of people, maybe 20 or 30% who have a spectacular response to chemotherapy that can prove durable, that is, can last more than a year. Dan Tetrolac at Columbia and Thomas Beer at

University of Oregon had developed a method of using Taxotere intermittently with these patients, just like we use intermittent hormonal therapy. So, you put someone on Taxotere, they have a nice, marvelous response, and the PSA goes down under 4 ng/ml, is what they use. Then you stop the hormonal therapy and many patients can go 12 months before they need to go on chemotherapy again. This favorable subgroups of patients. In fact, Dan Petrolac showed that if you are off Taxotere for more than six months, your cancer is going to be sensitive again to it. The resistance to Taxotere is temporary. So, there are a group of people who can go on for several years with Taxotere for six weeks and then nothing for six to 12 months, and then another course of chemotherapy. So, going on chemotherapy isn't necessarily a death sentence, but it is a change. The major pitfall with chemotherapy is it's inability to eliminate the rapidly proliferating pool that can replenish the cancer. So, the most important thing with chemotherapy is to find ways to slow the regrowth of the cancer. This keeps...this is a theme that keeps recurring. So, agents that effect that rapidly proliferating pool are important after hormonal therapy and after chemotherapy the same way they are in a PSA only recurrence. You are always looking for ways to turn down the malignancy. So, again the tools are the same...the Mediterranean heart-healthy diet, Avodart, Celebrex. We are finding more aggressive treatment like Sutent that blocks angiogenesis completely can help maintain remissions in people with aggressive disease. Leukin is a very valuable tool in prolonging the time off chemotherapy. Resveratrol we mentioned earlier works for some patients. We have a set of tools that we can use to prolong that period of time between chemotherapy options. Now, there are a group of chemotherapy agents in the wings that look very exciting, Phenoxodiol, which is being tested at Yale. The active dose is without side effects. It is an oral chemotherapy drug with no side effects. It is in phase II testing now. We are all waiting with baited breath for that. There are a bunch of other agents out there at various stages in development.

**Q:** A couple of questions about prostate surgery. I will lump them all together. Basically pertaining to the difference between a robotic prostatectomy and... if that is better than a radical prostatectomy in terms of recurrence. I think Dr. Dattoli brought up some of that. I would like to throw my two-cents in on that as well. Robotic prostatectomy...we are really still in the infancy of that. I think we are only five or six years into the true robotic age. That early study that Dr. Dattoli showed actually, when you really looked at that, a lot of the guys were in their learning curves. So, the problem with robotic surgery, which everybody realizes is, that everybody is

trying to learn it at a later stage in life. It is technically a little different than working on the prostate. Dr. Barzel and I probably lost count after about a thousand radical prostatectomies the old-fashioned way, which is still a very good operation. But, when we elected to start a robotics program here, we were smart enough not to learn it ourselves, because we didn't live in the video age. We don't have those skills, so we got Dr. Robert Cary join us a couple of years ago and he has already done, I think, close to 300 and is about to publish his first 220. Having lived through those, he was already pre-trained, so he had gone through his learning curve and the results, I think, you will see of doctors, who are very experienced, and that is the key. Anybody who does anything, surgical, radiation, whatever, has to be experienced. But when you see an experienced group of doctors who are doing that procedure, I think you will see less and less recurrence rate and I think it is a very good operation. Any more comments.

**A:** I have been very impressed about the quality of life advantage. In the patients who come to me after standard surgery versus the robotic surgery, the quality of life seems to be better after robotic surgery. But the patients I am seeing are mainly coming from Tuwari, New York, and Minin, who have had a lot of experience. I think for someone with organ-confined disease, I am really amazed at how quickly they recover and how minimal the side effects are.

**Another panel member:** Another comment about that was we talked about, I will throw in salvage radical prostatectomy, every urologist I like to say has done three. They do the first one. They can't believe how bad it is. They do one more. Maybe it is a little better. Then after the third, they finally realize this is not something to be done. There are some groups, like Sloan Kettering, where they do a lot of them, and even they will admit that is not for the faint of heart. Will robotics change that? I don't know. Dr. Cary did his first one recently and it went very well, but that remains to be seen.

**Dr. Barzel:** I think there are two factors with robotic and open surgery, etc. There is a definite learning curve. The industry...their self-interest is to sell as many robotic machines as possible and train as many doctors. I think you need to do at least 100 of anything before you get good. So, I think initial reports are not going to be as good. There is no way. I have a friend at Vanderbilt who has done about 2000 open radical prostatectomies and about 2000 robotics and got him in the corner after a couple of drinks and said come on now Jay, tell me the truth. What is the story? He is convinced that he can do as good as job robotic that he did open, but he had to do a lot, 200 or 300 before he got to that level. So, that is one issue. The other issue is that, an

issue that Dr. Dattoli alluded to, is that you are always fighting when you do a radical prostatectomy, and I have done over 2000 open radical prostatectomies, between making sure that you don't leave cancer behind and trying to preserve the neurovascular bundle. If you err on the wrong side, you are going to have a positive margin. And if you make some promise to the patient that you are going to potent and the patient says, look, I am only here because I want to be potent. I usually will not take a patient like that, say look, I can't guarantee it. I am going to have to do what has to be done. But, when you have already made that commitment and you go in, there is a very fine line. I think that is the issue. But, I think robotic prostatectomy will become the gold standard of care, no question. It is the standard of care in institutions that do a lot of them. It may not be the standard of care where people are just starting to learn how to do it.

Another panel member: Just to play devil's advocate here, Dr. Towari will tell you that between 30 to 50% of his cases that he goes in to do robotic surgery, he has to abort that procedure to an open procedure. That really just has to do with working in the well of the pelvis, the confines of the prostate, all the neuro vasculature surrounding and such. So, you may not always get what you thought you were going in to find. The article that I sited from the Journal of Clinical Oncology was a compilation of numerous studies. What it basically did show was that it appeared to be an improvement with experience with the operators, but it also had plenty of legs from the standpoint of the mavins, so to speak, of prostate surgery, be it Patrick Walsh at Johns Hopkins or Scardino at Sloan Kettering, who would basically say that in their experience that, and they said they did both, how true that is, I don't know, Eastman as well at Sloan Kettering, that they were more confident that when they were removing the prostate from the standpoint of surgical margins, that they can actually feel maybe some grittiness, some abnormality, that they otherwise wouldn't have seen because they couldn't have felt it with the robotic surgery. So, again, I think it really...time is going to tell.

**Q: I know there are some other questions. So, here is the deal. These gentlemen have been kind enough to spend their whole morning. I think we have had three world-class discussions.**

**(End)**