

# MAN TO MAN – SARASOTA

## Prostate Cancer Patient Support

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Man to Man

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

Our presenter for November 2007 is Steve Mamus, M.D. Dr. Mamus graduated with honors from Harvard and earned his M.D. from the State University of New York at Syracuse. He interned and completed his residency in Internal Medicine at Rush-Presbyterian St. Luke's Hospital in Chicago, and completed his fellowship in Hematology/Oncology at the University of Minnesota Hospital. Dr. Mamus practiced at Orlando Cancer Center, M.D. Anderson Cancer Center – Orlando, and currently with the Cancer Center of Sarasota.

### Introduction

I'm going to look at prostate cancer a great deal differently than surgeons, and a great deal differently than radiation oncologists. My college background is in microbiology, and when I was at the University of Minnesota, I worked with a lot of stem cell physiology. Actually, I was going to go into academic medicine before I decided to come to Florida. From my vantage point, I am less interested in whether somebody has received proton beam, IMRT, external beam radiation, or hormone manipulation. However, I am a great deal more interested in trying to understand the basic biology of what occurs both in prostate cancer, as well as other malignancies. Although it is important what treatment you get, I think it's probably more important understanding the basic biology of the cancer that you have. It may well be that if you have prostate cancer which is **biologically quiet**, that you will do well no matter what treatment you get. On the other hand if you have a **biologically aggressive** cancer, then whether you have a certain type of radiation with a certain doctor at a certain institution may not make that great of a difference. You may end up recurring, less because of which doctor treated you or what treatment you received, and more because of the inherent biology of the cancer.

### Molecular Profiling – Cancer Characteristics

Let's just step aside for a second. I know we are here to talk about prostate cancer, but I'm going to do something a little radical here. I'm going to talk about breast cancer for a moment; very similar illnesses, both hormonally driven. Whatever information we have on prostate cancer you can multiply it by twenty for what we know about breast cancer. If you

have a newly diagnosed early stage one breast cancer, (small cancer, negative lymph glands) you can actually predict from the tissue block, how that patient will do over the next ten years. This can be accomplished with molecular profiling, to predict how high a risk somebody will be for recurrence. These tests are commercially available, approved by Medicare, and by many of the major carriers in the State of Florida.

And, to be very specific, if you take an early stage-one breast cancer patient, which is defined as someone with a tumor less than two centimeters and negative lymph nodes; about 40% of those patients will be resistant to chemotherapy. And, by resistance, I mean they will not have benefit from chemotherapy. How is that possible? It's possible because those tumors, in these particular individuals, have such low recurrence rates before you do anything, that there is no possibility that you are going to have any meaningful impact from chemotherapy. And again, to be more specific, about 40% of patients with breast cancer have recurrence rates of less than 7%. Further, we make another assumption that they are going to receive at least five years of Tamoxifen. These are patients that are hormonally positive. It has been shown in several very large studies that those patients, not only do not need to receive chemotherapy, but there's no possible benefit that they can receive. So, you can pat yourself on the head and say we gave the patient chemotherapy and the patient did great. The patient was going to do great before you did anything.

The importance of molecular profiling is to tell us in which patients' chemotherapy is unnecessary. It also can predict which patients will not respond to hormonal therapy. And, this gene profiling is completely independent of the size of the cancer, the particular characteristics of the cancer, whether the cancer is well or poorly differentiated, and whether it is negative or receptive positive. So, it is an independent prognosticator. You can make decisions based on that how to treat a patient. As I said, when patients do well or poorly with their cancer; although we focus a lot about which treatment was done and which doctor was involved, if the patient did well, the doctor is a genius, or if I did poorly, well I just saw the

wrong doctor and got the wrong treatment. There may be some element of truth to that. But, probably the bigger truth is that if they have a more fundamental understanding of the biology of the cancer as to how dangerous it is, then that tells us a lot about what we need to do. Furthermore, as we all know, any treatment that you have for cancer whether it is surgery, whether it is radiation, whether it be hormones, or whether it be chemo, all of those things have a price tag. I'm not talking about money; I'm talking about side effects of treatment. So, if you can "tailor-make" your treatment program to give treatment where it's needed, or to not give treatment where it's useless, and where you avoid expense as well as potential side effects. These are good things!

### **What causes prostate cancer in humans?**

I'm sure everybody's thought about it. I see all types of oncology patients, and a very common question is.... why did I get this? Most of the time we don't know. Prostate cancer is interesting. First of all, this is a very, very common cancer. In fact, in men it is the most common cancer that is seen. The prevalence of it in populations is very high. It's age dependent. If you do autopsy series on men in their twenties and thirties, you will find prostate cancer in a certain percentage of those men. And, the prostate cancer may be invasive prostate cancer, or it may be PIN, which is a non-invasive form of prostate cancer. The chance of finding prostate cancer in men over seventy goes up to eighty percent. Now again, this is in autopsy series where they have carefully dissected, and looked specifically for the cytological evidence. We know that over the age of seventy, it may seem like every friend and neighbor that you know has some form of cancer. The fact of matter is, that prostate cancer clinically evident during someone's lifetime, is a great deal lower than this. What this tells us is the majority of prostate cancer which occurs in humans is sub-clinical. I think that right then and there this tells us something. It tells us that the majority of prostate cancer which occurs is sub-clinical does not trouble the patient during their lifetime. In fact, they don't ever know that they have the illness. So, I think that should give you pause when you are diagnosing somebody with prostate cancer as to when you are going to treat.

I also want to point out something else; going back to our breast cancer story. In breast cancer there is one published series of untreated breast cancer patients that was published in about 1908. The article appeared in *Lancet*, which is the British equivalent of the *New England Journal of Medicine*. If you take a series of women who have breast cancer and do not treat them; at twenty years about 8% to 10% of those women will be alive. So, that again tells you that there are a certain category of patients who have potentially very dangerous illnesses, who can do well in some cases, simply because the pace of their illness is very slow.

### **Men Who Don't Develop Prostate Cancer**

Now, I just asked the question a second ago "What causes prostate cancer?" Well, that's one way of asking the question. If we ask the question a different way; "Are there men that do not develop prostate cancer?" And, I am not sure if

there's anybody in the audience who has thought about that. I don't think that I thought about that before preparing this talk. The answer is "yes".... If you were born with a deficiency in an enzyme called five-alpha-reductase. What happens to individuals who do not have this enzyme? Well, first of all, we know there is a strong association between having the presence of testosterone and the risk of developing prostate cancer. One of the main drivers in the way people talk about it is the prostate specific antigen, or PSA. What drives PSA is testosterone. What's actually more important than testosterone is something called dihydroxy testosterone or DHT. This is twenty to thirty times more powerful than testosterone.

Every person who I see in the office as a new prostate cancer patient, I measure a number of things; not only testosterone levels but also DHT levels. For individuals who have an absence of five-alpha-reductase, these individuals are unable to convert testosterone to super testosterone, which is DHT. What happens if you cannot do this conversion? Individuals who have five-alpha-reductase deficiency have underdevelopment of the prostate (not a big surprise because you have less of a testosterone effect), undetectable PSA levels, and no evidence of prostate epithelium in prostate biopsies. The tumors start from the epithelia (the surface lining of the prostate) so there is nothing there to turn into cancer. Not surprisingly, they fail to develop BPH or prostate cancer.

### **Why Is This Important?**

Who cares about this? Well, we care! For example, instead of completely blocking this enzyme, what if we block it a little bit? If we can decrease five-alpha-reductase somewhat, could we decrease the risk of BPH, urinary retention, or prostate cancer? It sounds logical. You already have nature's biological experiment with individuals who lack the enzyme. Let's say that a lot of the enzyme is not so great in terms of the risk for prostate cancer. What happens if you decrease this? Finasteride, or Proscar, blocks the conversion, not completely, but it does block the conversion of testosterone to DHT. Studies have indicated that the use of Proscar reduced the risk of urinary retention and need for BPH related surgery by 50%. That was from one study termed "Proscar Long Term Efficacy and Safety Studies". I did not see the issue of osteoporosis addressed in this study. I suspect that the risk of osteoporosis for long term use of these agents probably goes up since you're decreasing a testosterone effect.

Let's take it one step further. We just said that the use of these five-alpha-reductase inhibitors can decrease the risk of BPH (benign prostatic hypertrophy), or enlargement of the prostate. If we can decrease the size of the prostate, can we decrease the risk of getting cancer? There was a study that was done by SOG (Southwest Oncology Group). This was the prostate cancer prevention trial. On this study men over the age of fifty-five with normal digital rectal exam, PSA's of less than 3, were randomized to either placebo or 5 mg. of Proscar for seven years. What they found in this study was there was about 25% reduction in prostate cancer in individuals who took Proscar. You may say to yourself "well that sounds pretty good and maybe every man, once they start to get So-

cial Security, maybe should be put on this pill". But there are side effects, there are costs, there's increase in risk of erectile dysfunction, and probably increase risk of osteoporosis.

The other concern that was raised on this study was that although prostate cancer incidence was decreased; the Gleason Score was increased in the type patients who were diagnosed with prostate cancer.

But suffice to say the increase in the Gleason Score probably is an artifact. It is probably an over-interpretation of the Gleason Score by pathologists not accustomed to the biologic appearance of prostates that have been subjected to a deficiency in DHT. There is a lot of epidemiologic data to suggest that, this in fact is what is actually happening in these patients. There is probably not an increase in the Gleason Score. And, this is an important point because similar issues ...again going to the issue of breast cancer, some provocative studies show that we can decrease by 50% to 70 % the incidence of breast cancer in patients taking drugs like Tamoxifen or some of the newer drugs that are on the market. And, there is at least one study that showed that there was an increase in hormone receptor negative breast cancers. The question was raised whether this was pre-selecting for more invasive cancers that were dangerous. But, suffice it to say, that if you do inhibit five-alpha-reductase, you can reduce the chance of BPH, and you can definitely decrease the risk of developing prostate cancer.

#### **Are There Certain Men at Increased Risk?**

Now, lets ask the question a third way. "Are there men that are at increased risk for developing prostate cancer compared to other men their age?" The answer is yes. And, that might be a good starting point to figure out what actually is causing prostate cancer in at least some individuals. To this end, starting back in the 1950's, if not earlier, people started examining familial prostate cancer families. What is a prostate cancer family? It has several potential characteristics:

1. **Early onset of disease** – so if you see someone in their 30's or 40's with prostate cancer, this is something to think about. We certainly see those types of patients.
2. **Three or more family members affected** – should point out that for cases under the age of fifty-five for prostate cancer, that 43% of these cases are felt to be familial in nature. A lot of incidences are sporadic. This accounts for about 9% of all prostate cases, overall. But at least it gives us a place to start in trying to understand what it is about these families that causes an increase risk of prostate cancer. Because, if we can get a handle on that, and we can answer that question, then perhaps we can go to the more general question of providing some understanding for the majority of others in terms of causation.
3. **The genetics of hereditary prostate cancer** – Going back to the 1950's, at least from the 50's on, it was noted that in certain select families it appeared that prostate cancer "ran in the family." In prostate cancer, if you had identical versus non-identical twins was there a difference in how frequently prostate cancer occurred? The answer was yes. It is much

more common in identical twins to develop prostate cancer than in non-identical twins. This points to the issue that there must be, at least some component of genetics that has something to do with the development of prostate cancer.

#### **Gene Variations and Virus Connection**

An increased risk of prostate cancer has been identified with the familial susceptibility locus Hpc1. This increased risk of prostate cancer is linked to mutations in the structural gene for RNaseL. In Hpc1 families a single amino acid substitution, R462Q leads to reduced activity of the RNaseL enzyme and can double the risk of prostate cancer. Individuals with the QQ (homozygous R462Q) genotype make up 11% of the population. This is work that was recently done at the Cleveland Clinic. Why is this gene important? This is interesting, and is in the realm of molecular biology, but we'll put it in layman's terms. Consider that this gene is likened to a "Border Patrol" or "Coast Guard" to protect itself from viral infection. If a virus infects the cell, this gene shreds or breaks down the invading genetic material that comes into that cell. It then marks that cell for the immune system to destroy it. This is true whether it's for an influenza virus, HIV, Avian Flu virus; it does not matter. This is a very broad mechanism of action. If you have genetic material introduced into a cell, the only way that is going to happen is by a virus invading a cell. This particular chemical will break down that invading DNA, which is important, because if it doesn't break it down, it may not only affect that cell, but the whole body. The way these viruses work, whether it is flu virus, or it's a tumor; the virus affects the cell and takes over the genetic machinery of that cell and derails it to make the cell do what the virus wants, which is to re-produce itself. This can make the cell explode with thousands or millions of viruses coming out of it.

Does the decreased ability to fight viral infection cause prostate cancer? How do we find out? Is this a big deal? Well, it is a big deal only if we think that prostate cancer is caused by a virus. If you have a defective defense system for viruses and if a virus has nothing to do with prostate cancer; it may be very interesting for other issues like getting viral infections and getting colds. It may not have anything to do with prostate cancer. But, here at least is a logical mechanism, if we are thinking that a virus might cause prostate cancer. If you have a defective ability to fight viruses which is genetic, it would seem like you may be set up for developing prostate cancer.

#### **Retrovirus Involvement in Cancer**

I want to take a quick aside here for a second to mention the issue of retrovirus infection. A retrovirus is actually a RNA virus which invades the cell and has a specific enzyme which allows it to produce DNA. The enzyme is called reverse-transcriptase. In the 1970's two people received the Noble Prize for that. What is also very interesting, and a lot of people don't realize this, is that the first viral cause proven in animals to cause cancer occurred nearly one hundred years ago. One of the concepts that we are going to be taking about today is that you can vaccinate your cat against getting leukemia. That leukemia is the same leukemia that occurs in children. We're

sitting now fifty years after the fact that this was demonstrated and we cannot vaccinate our children so they do not get leukemia. But, we can do it for our cats. We can now, however, vaccinate our daughters, so that they might possibly have a decreased risk of getting cervical cancer from a virus.

I just a second ago said that the patients who had an increased risk of prostate cancer had something wrong with the ability to fight a virus infection. If we think that is important, how do we look for it? There are over twenty thousand viral sequences that are known in these large libraries that are built by Biotech Institutes. And, you can have at your disposal something called a viral chip. This is a computer-generated technology where you can look at genetic sequence from over twenty thousand viruses. People may have heard of Avian Flu. Remember the Avian Flu outbreak about two years ago. They couldn't tell when Avian Flu first broke out, what kind of virus it was. Using this technology in a long weekend at the University of California at San Francisco, in less than seventy-two hours, they were able to identify what type of virus the Avian Virus was.

So, this technology has been used in patients who have this particular genetic defect. They have looked for a virus presence in those patients. And low and behold, they have found that in at least 40% of these QQ patients (2 gene or homozygous RNaseL deficient) contained sequences corresponding to a murine (mouse) retrovirus that causes leukemia in mice. This is what is really interesting about this retrovirus. When they did the gene testing on this, they found that it was something called XMRV. XMRV is a xenotropic murine leukemia virus. This virus which is being found in humans with prostate cancer, is very, very similar in genitive makeup to a virus which causes leukemia in mice. Xenotropic means that this virus is able to invade cells other than mouse cells.

Now, you may say to yourselves. Who cares about this? Why is this important? We've heard of HIV. I don't know if people in the audience are aware but there cases now well documented that HIV probably first occurred back in the 1950's. There was a case back about 1952 in St. Louis, involving a wasting death of a young black man. The pathologist had no idea what the heck was going on. He knew that it was something that they had never seen before. The pathologist froze the serum on this patient. Thirty-five years later when there was an assay for HIV; they tested it and found it to be HIV. This was published in JAMA about two or three years ago. In the 1950's there was an outbreak of wasting deaths in Holland and they suspect that this was probably a case of HIV. What's interesting about retroviruses is, when they first start out, they do not have much mutability, and they can be killed very quickly.

One of the greatest infections appearing in the world right now is the Avian Flu virus which will mutate, and it will be able to be easily transmitted from birds to humans. It's not a question that whether it's going to happen; it is a question of when. And when that happens we will probably have a pandemic like we had during World War I. This is the great fear. This is

again a retrovirus. When these viruses mutate they can become very aggressive.

Also, the other thing which is important, you cannot vaccinate your child to prevent acute leukemia. Why is that? Why can't we vaccinate people so they don't get HIV? Because the virus, especially HIV, is mutating so rapidly you cannot get a target that changes so rapidly. This is a very interesting finding, very provocative.

So, just to back track, I know that this is a little different than what people were expecting. I'm pointing out to you that in the 10% of patients with the familial form of prostate cancer some have been identified to have a defective ability to fight a particular virus. This virus is present in the surrounding tissues of the prostate cancer and occurs at least in 40% of these patients. What's interesting is that this virus is not found right in the prostate cancer itself, but in the surrounding tissues around it. I should also tell you that this virus has been easily passed in prostate cancer cell lines. We think that this may be one of several things that may need to occur for prostate cancer to happen. So, there may be more than one event here.

Just to summarize this. This is a **new** human retrovirus, and is the first retrovirus which has been documented to be involved with human infection with the retrovirus that is common to mice. We have not definitely proved that this causes prostate cancer, but, suffice it to say that we are extraordinarily close to having a viral causation for this illness. Having a specific gene mutation which compromises the natural ability to fight against virus infection, however, is increasingly suspect. XMRV infection as it might relate to prostate cancer is being looked at from a molecular biology point of view, but is still an open question. But, I say it has high probability.

### **The Question of Vaccines**

If it is a cause, directly or indirectly, the next question obviously is; if we can have a vaccine to prevent cervical cancer, can we develop a vaccine against XMRV?

Another interesting question being, what is the defect that occurs? The defect that occurs in these patients is that they cannot produce interferon. Interferon is an anti-viral agent.

I'm sure some of the people in the audience here have heard about the recent prostate cancer vaccine. That prostate cancer vaccine has several antigens taken from several prostate cell lines. It also has the genetic material to increase production of something called "Colony Stimulating Factor." Colony Stimulating Factor is an immune hormone that increases your white count. And, it does other things biologically. You can give Colony stimulating factor in the clinic to patients on chemotherapy to increase their white blood cell counts. Why are we giving that to somebody with prostate cancer? I believe the Colony Stimulating Factor increases the production of interferon.

A retrovirus can actually be genetically inherited. We believe that humans have a certain amount of retroviral material that serves one purpose or another. So, this can become a very sophisticated and very unusual type of infection. Now, the question is, does XMRV cause other cancers and infection in humans? We don't know, nor do we know what its origin is? Did this come from mice to begin with, and then mutated and

got into humans? Probably, because we think that HIV started in chimpanzees or apes, then mutated and turned into a virus which became more virulent and then was able to cross species barriers.

And again, the thing that keeps coming back to mind here is the Avian Flu. Avian Flu is a virus of birds. We know that some people have died. We know the mortality rate with this infection is around 50% to 70%. And, I would again tell you that as soon as this virus mutates more, it will do several things. It will make the transition from being able to go more easily from birds to humans. The second thing is, then it will be easily transmitted from human to human, then you are going to have a disaster. And, I think most of the world understands that.

#### **A Brief Review**

I talked a little bit about causation. I talked a little bit about hormonal causes for prostate cancer. I talked a little bit about genetic defects and the immune system being a cause for prostate cancer. Also I talked about the possibility of a retrovirus being involved in some way, in a significant minority of patients with prostate cancer.

We are going to switch gears for right now. And, I'm going to get back to what I first started talking about initially. I think it is important to understand the biology of the illness we are dealing with and how it might be prevented. In many cases, for example, it is much easier to prevent HIV than to treat it.

So, if we can prevent HIV, or prevent cervical cancer by a vaccine, or prevent feline leukemia virus by giving a vaccine, that's a whole lot easier than treating the illness. So, in some of these cases, the illness may take much, much longer for science to ever figure out the cure for the problem. If we can figure out what causes the problem, prevent it in the first place, we will be better off. The same thing with lung cancer, if we don't smoke we have less lung cancer. In fact I can tell you that I can remember when one of my professor at Syracuse, telling me this, that in the late 1800's early 1900's at Kings College in London, there was this hush silence in an autopsy. This professor was bringing in students to see something extraordinarily rare, a case of lung cancer. Nobody was smoking at that time. He told people that this was something you may not see in your professional lifetime. Times have changed obviously, and not for the better.

#### **The Need for Prognostic Indicators**

One third of patients undergoing prostatectomy for organ-confined disease will relapse. That's from a 2003 Journal of Urology. The challenge is to distinguish high risk from low risk prostate cancer.

Let's talk about if you have had a primary treatment for prostate cancer, and then you had a biochemical recurrence. One of the common problems that we see in patients with prostate cancer is what do we do when we have a biochemical relapse; a rising PSA? You do a ProstaScint, you do a PEG, a PET scan, a CT scan, an MRI, but you can't find anything. The question really is, after you have a biochemical recurrence following radical prostatectomy; what is the significance? What are we treating when somebody has a recurrence I think what you have to ask yourself is, "how serious is the problem,

and what are the consequences of the proposed treatment?" You may say that if somebody has an increasing PSA after a radical prostatectomy, it is a disaster. You think that everybody under those circumstances has to be automatically treated, and that everybody is going to do poorly. That is simply not true.

I know this can be a little confusing. Let me give a good example. Let's say five years ago you had a radical prostatectomy, up until now your PSA was zero, zero, and zero. Then all of a sudden you're out five years, and the PSA comes back two, or five. What do you do? How do you react to that? You go to your doctor and ask, what does this mean? How long am I going to live? Let's say that your surgery was five years ago.

Now, a review on what a Gleason Score is all about. A Gleason score is a very specific way of looking at the original prostate cancer when you were diagnosed. It looks at a number of different cellular characteristics under a microscope, and assigns a value of risk. A PSA of less than eight is more favorable; eight or higher is higher risk for recurrence, either local recurrence or distant metastasis. So, let's say that five years ago you had your radical prostatectomy, and let's just say for argument sake that your Gleason Score was six. So, it is less than eight. And, let's say that your PSA doubling time is a year. Let's say you did a PSA and it was two in January of last year, and in January of this year it was three. Are there patients like that where it goes up by one each year? Yes. If you have a PSA doubling time of one year and your initial Gleason score was, say six; it was less than eight. Your chance of being alive in five years is 99%. Your chance of being alive at fifteen years, having a PSA doubling time of one year, is 86%. At ten years it is 95%.

So, why is this important? Let's take a different example. Let's take a worst case scenario. Let's say your surgery was a year ago and let's say your Gleason Score was nine. And, let's say your doubling time was less than three months. That means the PSA goes from two to four in say a month or two. The five-year survival for those patients is only 51%. And, the survival in fifteen years is less than 1%. So, what does this tell us? What this tells us is that if you just say that you have a recurrence of the PSA in a vacuum, and say nothing else; it is pretty meaningless.

#### **In Summation**

What's important in my opinion is to know what your PSA doubling time is. People will ask when you start treating patients with a rising PSA. Is it at a PSA of five, is it ten, or is it at twenty? It's none of those. It doesn't make a difference what the actual PSA value is. What is important is how quickly that PSA is doubling. That gives you a pace of the disease. Why is this important? Because, what this tells us is that the patients who have high Gleason Scores, and have PSA doubling times that are very low; a couple of months as an example, those are the patients that are in need of intervention. You may say, well everybody needs intervention, because if you have a detectable PSA that's abnormal, it's coming up; that's a bad thing. It is a bad thing. But, it's a relative bad thing because the problem is; it's not a "free lunch."

The problem is that the treatment for recurrent prostate cancer involves the metabolic complications of androgen deprivation therapy. At the last National Oncology Meeting in May; it was discussed that we should no longer approach men over seventy with prostate cancer, in an indiscriminate manner, by putting them on hormone deprivation therapy for the rest of their lives. That being, whether they have metastatic disease, recurring PSA elevation, or high-risk prostate cancer at time of diagnosis. Metabolic syndrome includes an increased tendency towards diabetes, insulin resistance, and hyperlipidemia. If your risk of prostate cancer killing you is 3% within fifteen years, and you've had triple bypass surgery, had five coronary stents, two strokes, and you are diabetic, and your cholesterol is six hundred; guess what? Prostate cancer is not your biggest problem in life. And, so what I am saying to the high risk patient over 70 years of age, we'll treat with hormone deprivation for six months, and then see where we are in life. The standard for younger person at high risk would be three or five years of continuous hormone deprivation.

By automatically putting all of these patients on continuous, indiscriminate treatment with Lupron or Zoladex which decrease your testosterone level, two considerations need to be looked at. 1. Two leading authorities speaking at the National Prostate Cancer Conferences found that the mortality rate at

five years was decreased by about 18% for people who start on hormone manipulation immediately. 2. But, they had a 15% increase in cardiovascular events, and an increased potential of developing osteoporosis. I am not suggesting that we do not use these agents, but I think we have to use these agents with greater restraint. And, I think we have to weigh what the actual risk of a prostate cancer, in terms of how dangerous it is, versus what else medically is going on with the patient. There are not that many patients that we are seeing with prostate cancer, with that being their only medical problem. I think I'll end there.

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*Editor's note: The complete transcripts of the preceding edited talks are available (via email only) by contacting Marion Stuart, [marion.stuart@cancer.org](mailto:marion.stuart@cancer.org).*

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