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**Session 6: The Future of Men's and Women's
Urologic Health – Karl J. Kreder, MD, MBA**

[START Day 4 Sessions 6 and 7.mp3]

[Background conversations]

DR. CRAWFORD: Final round up here of FDUS. It's been a great meeting, a lot of good discussions. We appreciate all of the support and everybody being here. No matter what we do people leave the last day, if it's the last afternoon, last morning, last whatever, people just have this thing about leaving. So a lot of people left this morning even though we have a lot of exciting stuff on including things that were supposed to be people from industry here, castrate resistant. So that hasn't worked either but we have some diehard supporters. We appreciate it. And we will probably finish up at 11:00 it looks like and maybe before. I know some people are trying to get out. So I'm going to turn it over to my good friend Karl Kreder. I introduced him yesterday. Karl is going to talk about the future of men's and women's health, moderate that, have a couple of discussions. We won't have a talk on BPH since Jerry is not here. We can have some discussion about it. So Karl?

KARL KREDER, MD, MBA: Well thanks David and thanks for the kind invitation on this meeting. It's a great place. I haven't been to the Broadmoor in 25 years. I'll make sure it's not that long before I come again.

So this morning we're going to start off with a lecture on the future of testosterone placement therapy and Jerry is not here but an article came out last night in JAMA that goes straight to the heart of this testosterone controversy. So we'll have these two talks. We'll talk a little bit about that article. I think Marty's going to cover that a little bit. And then I'll talk about the future of female urology and we'll have some discussion and then start the next session.

So the first lecture is going to be by Marty Miner, "The Future of Testosterone Replacement Therapy".

Featured Lecture: The Future of TRT - Martin Miner, MD

MARTIN MINOR, MD: It's always a pleasure to be here and this is such a wonderful gathering, and I learned so much and am so grateful as a primary care clinician to participate in this.

So I'm going to speak about testosterone and was asked to talk about the future of testosterone which is an interesting way of framing it. So I wanted to start with in an ideal world what would happen with testosterone prescribing and if you look at these domains you'd see that awareness, education, patient expectations, labeling guidance, diagnosis, promotion, and marketing, and research, and new paradigms would all intersect appropriately and you'd have a perfect prescribing pattern. The trouble is that shortcomings in any one of these domains of course leads to, can lead to chaos and we've had shortcomings in several domains in the testosterone world, and there's been rather a bit of a quagmire.

So the considerations that we have now and concerns are are we prescribing appropriately to the right patient with a confirmed diagnosis? Are we following present treatment protocols that exist? Are we checking follow-up testosterone levels, hematocrits? Are we repleting levels to normal or midrange? Are we monitoring T levels and starting replacement therapy? Because it's very important to establish compliance effectiveness and adverse events.

Now and Mo is going to go over the studies that have been, the controversial studies, and in relationship to testosterone and cardiovascular issues, and a lot of these deal with a lot of these problems.

There have been significant, there's been a lot of change in testosterone, testosterone prescribing, the perception of testosterone over the last spring, and the FDA mandated as we know label changes in May of this year. Testosterone is indicated for replacement therapy in conditions associated with the deficiency or the absence of endogenous testosterone. Low levels that are due to disorders of the pituitary gland or brain that cause this, which are, or the testicles which is called or known as classical

hypogonadism, but the FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone levels due to no apparent reason other than aging. And we know that levels decrease, especially free testosterone, as men age. And the benefits and the safety of this use have not been established.

So when you look in the labeling issues you see that the manufacturers of all approved prescription testosterone products had to change their labeling in May of this year to clarify approved uses of the medication. And this required that these manufacturers add information about a possible increased risk of heart attacks and strokes in patients taking testosterone, although there's a great deal of controversy whether this exists at all, and actually a belief of many that testosterone reduces atherosclerosis or has a negative impact.

We also know that healthcare providers should prescribe therapy for men with two confirmed low levels caused by certain medical conditions and replicated by laboratory testing. The FDA also convened an advisory panel in September of 2014 and it's too bad that Dr. Garnick is not here right now because he was--

DR. CRAWFORD: Yeah it is because he was a negative thing there.

DR. MINER: He was, well he was on the panel and between, the panel was concerned about several issues and I'm going to quickly summarize them. Between 2010 and 2013 the number of patients receiving testosterone increased from 1.3 million to 2.3 million with 60% prescribed by primary care clinicians. And in a sample of 250,000 men only 72% had a claim submitted for testosterone levels prior to receiving therapy. 21% never had a claim, 6% had a claim submitted after the initial diagnosis, and no study has documented whether or not these levels were low. In another study there were fewer than 50% of men that received testing prior to the initiation of therapy. So clearly there is a problem with guidance or prescribing.

Testosterone was originally intended for men with no endogenous testosterone and the clinical benefit data were not required for regulatory approval as these were well accepted. So the FDA never used clinical data in approving

these products. And instead the FDA requires only pharmacokinetic parameters for testosterone approval. That's 75% of men have to achieve a level between 300 and 1,000 ng/dL. Clinical efficacy endpoints are considered exploratory and implicit in this is that providers or clinicians would measure both a basal and post therapy value. And not testing cannot be justified. So there is a great concern that in this country that almost 50% of men were receiving testosterone without prior testing.

DR. CRAWFORD: I think what happens is that somebody might have a, like we do testosterones during Prostate Cancer Awareness Week. We send them the results.

DR. MINER: Right.

DR. CRAWFORD: They have it, they take it to their doctor, and they say okay, you know, I have all these symptoms and here's my T level. And they might not order one.

DR. MINER: Right. We don't know what accurately--

DR. CRAWFORD: And I bet that happens a lot.

DR. MINER: --reflects the actual real-world data, but this is what we have.

DR. CRAWFORD: Yeah.

DR. MINER: And clearly the FDA--

DR. CRAWFORD: Garbage in/garbage out.

DR. MINER: --approval process is not indicated for any age-related testosterone decline, and the panel that Dr. Garnick was part of voted 20 to 1 in favor of revising current indications by limiting testosterone use to those with what we call classical hypogonadism, and including this potential weak signal that they even acknowledge for cardiovascular risk.

If you look at, this is a labeling for Testopel, and we know that the more specific signs are the sexual parameters about libido, loss of spontaneous erections, and that the less specific signs are fatigue, which is often the sign that drives men to seek testosterone testing. But as you see with Testopel here there's difficulty understanding that the current labeling does not support the improvement of any one of these symptoms as an indication for

treatment. So that's very important that we're treating for clinical signs and symptoms but the current label has no clinical signs or symptoms in this.

In addition, the intended population for testosterone products were hypogonadal men with specific disease conditions, with the absent or deficient testosterone like Klinefelter's, pituitary injury, Kallmann syndrome. But product use data, real-world data showed a different real-world population. That middle aged men with low T or age-related hypogonadism were being treated specifically in the 40 to 60 year old age group, and that was never the intention for these products. But what I find difficult to understand and accept is that age related is often consistent with comorbid related. As men age they become obese. As men age they develop hypertension. As men age they develop type 2 diabetes. So this is part of their testosterone deficiency.

So of course current product labeling does not include age-related hypogonadism but current labeling did unintentionally imply such use by including idiopathic gonadotropin or LHRH deficiency, and this may still exist because the FDA replaced idiopathic with acquired hypogonadism, and it's yet to be definitively stated that T is not indicated for aging related clinical issues in men. Comorbid low testosterone is. Where does it stand? Where does it fit in secondary hypogonadism? That's part of the quagmire.

In terms of guidance the Endocrine Society gives us recommendations based on clinical signs and symptoms, two levels, and the presence of clinical signs and symptoms. The diagnosis is very difficult because clinicians we're told that we should use the lower limit of normal range for healthy young men and there's a wide variance that exists. The physician when confronted with a patient tries to make a diagnosis of hypogonadism with clinical guidelines creating an environment open to individual interpretation because they're confused along with everyone else about specific guidelines. Patients were made aware of low T through prior DTC ads and are eager and ready to obtain information, anything that's going to help them with an improved quality of life as they age.

So drug development does not support at this time the

presence of data to support the, for the use for age-related hypogonadism. It's unclear whether signs or symptoms of low testosterone reflect hypogonadism, and whether these signs and symptoms are the direct results of low testosterone, specifically fatigue, diminished sexual desire, muscular weakness, etcetera.

Evidence is needed to determine, to demonstrate that these signs and symptoms are part of hypogonadism. Evidence from well controlled trials is needed to show that repletion is safe in aging men, and the population and indications need to be clarified.

The sales of T products has plateaued but it's still a three-billion-dollar business. And the common marketing messages include that testosterone for treatment of sexual dysfunction and an increase in athletic performance and a feeling of wellbeing. And the last one thing that I should say is that the marketing of testosterone products has come under the purview of the FTC, the Federal Trade Commission, and not the FDA.

So in conclusion, clinicians have to manage expectations and focusing on the increase in sales is not really helpful to anyone. We're awaiting the results of publication of the T trial which should be established and published in the New England Journal of Medicine in the next month. This shows in men greater than 65 years of age it's a randomized controlled trial for one year that there were no signs of safety issues regarding cardiovascular disease. Prescription practice is consistent at this time with a current understanding of the diagnosis and management of hypogonadism, and there is a lot of polarization that my truth is better than yours. Hypogonadism is a true challenge. The diagnosis and the management of this condition remains unclear. The current prescribing pattern is a reflection of the condition that's in need of more collaborative work between medical professionals, and patient advocacy, regulatory authorities, and industry.

Thank you. And lastly you can see that - - . [Applause].

Featured Lecture: Controversies with TRT - Mohit Khera, MD, MBA, MPH

DR. KREDER: Well thanks. That was a nice summary and leads us into our next lecture. Mohit is going to talk about controversies with TRT, and there's certainly plenty to fill ten minutes.

MOHIT KHERA, MD, MBA, MPH: Well good morning. I first want to thank Dr. Crawford and the program committee for giving me the opportunity to discuss controversies in testosterone replacement therapy.

There are really four controversies, which I'm going to try to briefly discuss. The first one is the use of testosterone in the BPH, the use of testosterone in women for female sexual dysfunction, the use of testosterone and its effects on cardiovascular disease, and finally testosterone in prostate cancer. So we'll touch on these very briefly.

So if you open the package insert of any testosterone product you're going to find something very interesting. I want you to read the first line on any one of these products. It says, "Monitor patients with BPH for worsening of signs and symptoms of BPH." I'd like to say there is no data, there is no data to support this claim. This is a theoretical risk. In fact, if you look at the literature the literature would support that testosterone improves lowering urinary tract symptoms and BPH symptoms.

This is a study looking at 95 men receiving Nebido every 3 months for 12 months. As you can see over the course of a year not only do you see a significant improvement in IPSS scores there's a significant improvement in PVR as well in these patients. There's also an improvement in C-reactive protein suggesting that this is an anti-inflammatory effect of testosterone.

Even looking at five-year data giving testosterone to men, this is a German study showing again significant improvements in IPSS scores and voiding symptoms. So again, I question how we get that first statement in the package insert.

In terms of women we've been treating, testosterone was

first synthesized in 1939 by Butenandt and Ruzicka, but it's interesting that same year we actually started treating women with testosterone in 1939. Now realize that testosterone for FSD is not currently FDA approved, so we treat women off label. But the conversion is one to ten. Whatever dose I give to a man I give a woman one-tenth the dose.

There's no question that testosterone significantly improves sexual desire in women over placebo. These are two studies. And there's also no question that testosterone significantly improves sexual activity. If you look at the past four weeks in women receiving testosterone the amount of time they engage in sexual activity significantly goes up versus placebo.

And we focus much on estrogen and bisphosphonates and vitamin D for bone mineral density for women, but we don't really talk about testosterone. Testosterone is extremely important for reversing osteoporosis and increasing bone mineral density in women. This is a study looking at estrogen or estrogen plus testosterone in women. This is a two-year prospective study. Those women that receive estrogen plus testosterone had the greatest increase in bone mineral density, not estrogen alone.

So recently this past month I published a study, a review article on testosterone therapy for female sexual dysfunction and I talked about the myths. And there's four myths I'd like to discuss. First, there's no data to support that testosterone causes an increased risk of cardiovascular events in women. Second, there's no evidence to indicate that testosterone results in increased risk for endometrial or ovarian cancer, and finally there's no evidence to suggest that testosterone causes breast cancer. In fact, when I did the literature search there is some data so support that testosterone may be protective against breast cancer in women.

Now I don't think there's a single person in this room that hasn't seen these commercials. If you've had a heart attack and taken testosterone please call these attorneys, you're entitled to compensation. So where did they get this? It's a very interesting story. Realize I need to set the stage first. For the past ten years studies have shown that men with low testosterone levels are much more

likely to die at an earlier age. An interesting thought. So if you have low testosterone you're much more likely to die at an earlier age. If you look at the larger studies, these are many studies, over 500 patients, what they'll show you. And if you look at the last column is that men with lower testosterone levels are much more likely to die at an earlier age and most likely due to cardiovascular events. They're dying from a heart attack or a stroke.

So this is the data that we had for the past ten years. In fact, if you look at all of the studies prior to 2010 I can count 49 studies showing the beneficial effects of testosterone against cardiovascular disease.

Well something interesting happened in 2010. Dr. Basaria published a study in the New England Journal of Medicine, then there was 2013 the Vigen article, then in 2013 the Xu article, and then 2014 the Finkle article. Now I don't have time to go through each one of these in great detail, but each one of these suggested that testosterone may cause a heart attack or a stroke. And there are significant flaws with each of them but I'm going to focus on only two of them, the Vigen article and the Finkle article because those are the two articles that the FDA cited for the reason to put a warning in the label.

The Vigen article, no randomization or placebo. There were two major corrections to the article. The first version of the article actually showed and listed that those men getting testosterone had a lower risk for heart attack and stroke than those men not getting testosterone. They had to make a correction to correct it. They excluded over 1,100 men. When we asked them why they excluded 1,100 men they said you know what? We actually made a mistake. It was only 128 men. They were off by 1,000 men and they had 10% of those patients who were actually women, which was a big mistake as well. So they had to make a second correction. And because of those corrections 29 international societies asked for the retraction of this article and JAMA has yet to retract the article.

The Finkle article, no randomization or placebo. There's actually no control group and what they did is they went through a health insurance database and they looked at men before they started testosterone and only 90 days after they started testosterone, although they had data up to a

year. And what they found is that those men before testosterone and after testosterone the difference of an MI was a difference of 1 in 1,000. Again, no control group, no randomization, no placebo. But because of the Vigen article and the Finkle article we get this this past year where the FDA says that there is a possible increased risk for heart attack or stroke with use.

So after this FDA warning came out Dr. Marty Miner and myself and a few others published an article in the Mayo Clinic's - - where we actually went through every single article that was published on testosterone and cardiovascular disease and we came up with some conclusions. First, we showed that low testosterone levels were actually associated with increased risk for cardiovascular disease. We also found that severity of cardiovascular disease was inversely correlated with total testosterone and free testosterone. Testosterone therapy was associated with significant reduction of obesity and fat mass. Testosterone therapy improved the time to onset of symptomatic angina, and exercise capacity and peak oxygen consumption in men with CHF was significantly improved. And realize that all of this is based on level one or level two evidence.

And the last controversy, prostate cancer. So if you take a poll and you ask men throughout the world what is the number one reason why you do not give men testosterone? The number one reason is I am fearful that it will cause prostate cancer, throughout the world. But where did this come from? It actually started in 1941 when Huggins and Hodges in their seminal paper reported that reducing testosterone to castrate levels caused prostate cancer to regress. In that same article they said the administration of exogenous testosterone caused prostate cancer to grow. If you pull this article you'll find something very interesting. It's based on one single patient, one patient in 1941. In fact, if you said Dr. Khera can you please show me all of the articles that show that testosterone causes prostate cancer I would say I would not be able to produce one single article, yet it's the number one reason why urologists do not give men testosterone, for fear of prostate cancer.

So Dr. Crawford and I last year had the opportunity to publish an article looking at every single study that's out

there giving men testosterone after a history of prostate cancer, whether it be radiation, brachytherapy, and it was a review article. And the top four, believe it or not there's only four articles of getting testosterone to men after radical prostatectomy in the literature. That's it, that's all we have. And in fact we have only about five articles in giving testosterone to men after brachytherapy or radiation.

If you look at the last column you'll see if you look at cancer recurrence you'll see that the majority of these articles showed no cancer recurrence or progression. And in fact, in the Pastuszak brachytherapy article there were six recurrences but four of these men were high risk and high grade. And in the Pastuszak article in the prostate cancer four of those men had a recurrence, and these were high-grade men.

I just want to spend a moment talking about these articles. These are studies from my institution that we published. We actually treated men who were high risk. So we had men who were Gleason 8, positive nodes, we had positive surgical margins. These are high-risk patients. And we had 103 men. Of those 103 men we had 77 men who were low to intermediate risk, 26 men were high risk. They said doctor we would like to have testosterone, we're suffering from signs of hypogonadism. And we treated them.

We had a control group of 49 men, 15 men were high risk, 34 men were not high risk and we followed these men. Biochemical recurrences after 36 months were only seen in 12 men who were only in high risk. But the interesting thing I want to point out is that only four men, or 15% of those men who were high risk had a biochemical recurrence at 36 months. You should obviously think to yourself that's pretty low, 36 months for men with positive nodes, positive margins, and Gleason 8 or higher to have a biochemical recurrence. And 53% of those men in the control group had a biochemical recurrence at the end of 36 months in the control group. These were men that were not taking testosterone.

So if you add up all of the men who've received testosterone, if I count the abstracts and if I count the publications I can count roughly 500 men who've had testosterone after prostate cancer, and 10 of those men

actually had a recurrence, and that recurrence rate translates then to roughly 2% of men with a biochemical recurrence. Again, I want to strongly stress the fact that this is a very low biochemical recurrence and even in men who are high risk. And every time we submit these papers for publication the editor always says to me I don't believe it. Your recurrence rate is too low. Are you suggesting in any way that testosterone could be protective against the recurrence of prostate cancer? I think that's an interesting thought. If you look at the basic science literature there is data to support that maybe testosterone is protective against prostate cancer growth and may suppress prostate cancer growth.

I'm not going to go into these but I want to just go into some of the more clinical trials. This past year I had the opportunity to give grand rounds at John Hopkins, and a gentleman by the name of Dr. Denmeade treats prostate cancer resistant, prostate cancer with high doses of testosterone. So patients with metastatic prostate cancer who come in are treated with high doses of testosterone. And his recent article that he published he had 14 patients castrate-resistant prostate cancer treated with testosterone enanthate 400 mg every three months. So 50% of those men had reduction in their PSA, 50% of those men actually had significant radiographic improvement on x-ray and CT, again suggesting that testosterone may be even a treatment option for men with metastatic castrate-resistant prostate cancer.

And then finally a word on active surveillance. So as many of you know there's a movement in the United States to move to active surveillance and many of you will be approached by patients who have a low Gleason score, a low PSA and say doctor I know I have prostate cancer but I have low testosterone and I want to be treated with testosterone. That will come up. There have been several studies out there, one of ours, showing that treating men on active surveillance in our small series we had no cancer progression in any individual. In fact, there was no cancer identified in 54% of the patients on follow-up biopsy. We're currently conducting a study with MD Anderson looking at active surveillance but I think this will be more germane as time goes on.

So in conclusion, testosterone therapy has been shown to

improve BPH and LUTS. Testosterone therapy can safely be administered to women suffering from FSD. Low serum testosterone has been associated with an increased risk of MI and cardiovascular risk factors. And there's no convincing data to support that testosterone therapy causes prostate cancer. Thank you for your attention. [Applause]

DR. CRAWFORD: We're going to have some discussion. If that's the case all of this stuff why did the FDA panel say what they said? Both of you guys. If everything is so convincing why did Marc Garnick and the group shoot all this down?

DR. KHERA: Right. So the FDA said it's a possible is what you read carefully, it says it's a possible increased risk.

MALE VOICE: At weak signal.

DR. KHERA: A weak, and so what they're trying to say is that there could be some noise there, and there could be some noise there, and I agree that there needs to be more studies. But the way the public and the media reads this is that it causes cardiovascular disease when they see that warning.

DR. CRAWFORD: And - - lawyers.

DR. KHERA: And the lawyers.

DR. MINER: The FDA was most concerned about the one article, the Basaria article, which was a randomized controlled trial. It was a small trial. It was 200 men, well actually for testosterone it was a large trial, and it went for three years and it showed four significant adverse events, including MI, stroke, and death. But most, the majority of events were just pedal edema, and these were men who were very old, mean age of 74, receiving super physiologic levels because it was a mobility study. It was not powered to look at safety.

But the same study done by Sherena Shankivar [phonetic] also showed the absolute opposite. So the FDA was concerned about this weak signal, more than that I think the FDA was concerned about the fact that of the DTC the fact, the implications of that, the rapid rise in testosterone prescribing, and the lack of levels, according to Marc.

DR. CRAWFORD: Yeah?

MALE VOICE: Two points, first, you didn't present the con data on giving testosterone to men with castrate-resistant disease. And there's a study by Manning [phonetic] from a number of years ago where they actually had to do screening myelograms because these patients had developed cord compressions while they were getting this androgen priming. So I think this is a much, much more complex issue and it may be related to the different phenotypes.

Secondly, through all of this data that was presented this morning you really are not giving any practical guidelines to treating a man who walks into the office with a low testosterone level. And my question would be if you have somebody who is obese, may not be sleeping well, which are known factors to testosterone being low, would you not counsel them first to give them a period of time before you commit to them to what I think would be life-long therapy because once you give testosterone to somebody would not the testicles atrophy and then can you not get them off therapy at that particular point?

DR. MINER: You're absolutely correct. I counsel every patient. The number one comorbid state associated with testosterone depletion is obesity, and especially visceral adiposity. So each, the argument is made that if you get these men to exercise and follow their diets and reduce weight that their testosterone will normalize. The trouble is you can't get these guys off the couch and I tell these men that testosterone is a tool and that testosterone by itself without exercise and diet and lifestyle change has a very limited impact, although testosterone and obesity data is quite significant.

So it's always done in the setting of lifestyle discussion.

MALE VOICE: Right.

DR. MINER: With men under the age of 50 we start with clomiphine citrate to preserve testicular function right now. Men over the age of 50 who have issues of fertility or concerns about fertility also are started on clomiphine citrate. And you're right about lifelong, although that's not necessarily true for every man.

MALE VOICE: Okay.

DR. KHERA: So two comments on that. So absolutely try to treat the underlying condition. If patient has sleep apnea on chronic prednisone, on opioids, obesity, diabetes, that's treated first. If there's a significant improvement in their testosterone level then we're set because I do agree, testosterone is for life. So if you put someone on it you're committing them for a long period of time. So I agree with Marty, typically these patients I'll put them on clomiphene citrate and what we'll do is we'll elevate their LH and FSH while they're trying to lose the weight and they're trying to cure the sleep apnea.

And then the guidelines for after radical prostatectomy are different because it's somewhat controversial, but we do have guidelines that we use, and we currently are conducting an FDA-approved trial and the FDA is allowing us to treat men as long as they have a Gleason 3+4 or less, two undetectable PSAs within the first three months, which means I can treat the patient after three months, negative surgical margins, negative nodes. So I use that as a guideline to treat patients post radical.

DR. MINER: Lastly, there was a reference, oh I'm sorry.

MALE VOICE: No, go ahead.

DR. MINER: There was a reference to an article that was published yesterday in JAMA that was done by Dr. Bhasin. We have a couple of slides about that from the article, but in essence it was 302 men randomized to 7.5 grams of testosterone a day, of 1% testosterone versus placebo for three years and followed by CT calcium and CIMT carotid intimal wall thickness, and also all of the domains of sexual function. There was no increase in any atherosclerosis, there was no change in CT calcium scores. And also these were all men who were over the age of 65 years of age, and also there was no improvement in any of the sexual function domains, which is clearly in contrast with the T trial which is going to be published in the New England Journal of Medicine which does show an improvement in all sexual domains, a very strong improvement. So right now we're really left with a lot of conflicting information.

MALE VOICE: But the point is I think in the panel of the FDA as far as I understood people like Marc Garnick who is in my

view - - and if he would be here he would say the same but Marc Garnick is with all respect is not at least in international recognized as a testosterone expert. By the way, there were no urologists in that committee as far as I know.

DR. KHERA: I think there was one, Toby Chi [phonetic] but he doesn't do predominantly testosterone. He does incontinence.

MALE VOICE: I'm sorry?

DR. KHERA: He doesn't, there was on urologist--

MALE VOICE: There was no, that's what I'm saying. There are urologists or oncologic urologists who were experts in the field.

DR. KHERA: Yeah, right.

MALE VOICE: The same discussion took place in Europe with EMEA and EMEA did not give out a warning like the FDA has done. But there's also a difference in practice between the United States, and that probably has played a difference in practice between the United States and Europe. We for example we are doing a lot in - - institutes, we are doing a lot of testosterone replacement but we do it very, very, very strictly according to what you do and what you do, but in the United States are huge promotion campaigns and you could arrive five years ago in whatever airport in a major city and you saw billboards do you know your testosterone? Those billboards are gone now, but I mean the point is that urologists and oncologic urologists should take the responsibility to be as adequate as possible to diagnose low testosterone in the aging male population and to select patients that need treatment. And the first step when you find a low testosterone, the first step is not replacing testosterone because it will not have a major impact on sexual function. It has all the improvements that come first. But you should certainly select your patients and start with other measures such as life fitness programs and we are quite successful in that. We force them moreover because testosterone replacement is not reimbursed so patients are more inclined to do physical therapy and fitness programs to lose weight. On the other hand, I guess the big issue in Europe, partly in your presentation, that the LOH some of the endocrinologists say it doesn't

exist because it is a consequence of comorbidity. And what is first? Should you treat a comorbidity or should you replace testosterone?

DR. MINER: Well, that's the whole point is that my opinion is that you do both.

MALE VOICE: Yeah.

DR. MINER: And if you can wean a man off of testosterone that's fine but you do both simultaneously. You improve his diabetes at the same time. And what Mo said about sleep is very important because of the issue of sleep apnea and obstructive sleep apnea in the role, as a comorbid diagnosis is just almost like first cousins with testosterone deficiency.

The FDA even through its analysis said Finkle and Vigen were worthless studies, worthless studies, and the New York Times had a complete editorial by the entire editorial board that said we are dangerously hurting men in this country by prescribing testosterone. Testosterone is part of the life extension business or the T clinics, and it's one of those products along with human growth hormone and human chorionic gonadotropin that's given to men who can afford them on a cash basis. In this country now after the FDA's revisions we're having trouble getting testosterone covered for patients at this time.

DR. KHERA: There's no question that there is some abuse with testosterone. There's no question, in the U.S. more than anywhere in the world.

DR. MINER: No question.

DR. KHERA: And there are many young men who have perfectly normal testosterone levels that take testosterone because they want to feel better. Many of them don't know the fertility implications. They come into our office and they didn't know they've become infertile. Right? But there is a definite abuse and I think the FDA is concerned about the abuse.

DR. MINER: And 14% of urologists have prescribed testosterone for fertility.

DR. KHERA: IN AUA 26, yeah, yeah. The AUA sent out a questionnaire to all of the urologists and they said 26% of

the urologists in the questionnaire responded that they would treat men with testosterone while they were actively trying to achieve a pregnancy. They didn't know, which is a big problem.

DR. MINER: It's sad.

DR. VESTAL: Can I make a comment? It's taken years and years for us to get people to draw testosterone on our prostate cancer patients on hormone therapy. When will data be available for us to give testosterone or to draw testosterone on our post-prostatectomy, post-radiation patients so that we can feel confident that giving testosterone after primary therapy for prostate cancer will be a viable option?

DR. KHERA: So the problem is that we need a randomized placebo-controlled trial, and we're just starting to finish the randomized placebo-controlled trial in the normal population, not the post-prostatectomy patients. And we don't have that. We're starting one now. We have one at Baylor, the only one. We're looking at it but it's a small pilot, that's all it is and so the true answer is without that study you can't say with confidence that it's completely safe. You have to have the study.

MALE VOICE: Well it is, and it has been reviewed by the EAU guidelines panel on testosterone replacement and in the guidelines it says that after, around a year or two years, it's two years I believe, that if the PSA remains undetectable after radical prostatectomy and patient has clear symptoms of LOH you can replace testosterone in prostate cancer. And by the way your indication that you can give testosterone, high-dose testosterone in patients with advanced prostate cancer is not new. I remember that it was in the 70s and 60s it was very, prostate cancer in Sweden, advanced prostate cancer in Sweden is extremely frequent, and I remember urologists, all urologists in those days in patients who were progressing symptomatically that were given intravenous or intramuscularly high doses of testosterone and a number of those patients really improved. So there is clearly also an indication that testosterone replacement or testosterone administration can influence progression of prostate cancer.

DR. KHERA: So I agree with you. I agree that it's safe, and in

my lab and more further work I almost to some degree believe it's protective. I believe that men in the unilateral range are protected against the recurrence of prostate cancer. But we do live in a litigious society and I will tell you that if something went to court you'd have to say where are the articles showing that it's safe? And that's going to be hard to prove right now.

DR. VESTAL: So how many patients would it take to see safety with testosterone?

DR. KHERA: I think well over a thousand, and that's what they had in the T trial, and someone--

MALE VOICE: 800.

DR. KHERA: Yeah, they had 800 and it's got to be funded and since it's a small subset of the population the question is where would the funding come from? The T trial was how much? How much did the T trial end up costing? It was a billion. Right? Close to a billion dollars. Yeah.

DR. FINKELSTEIN: So along those lines, my partner Alvaro Martinez, who many of you know, submitted two years ago as I sit on the NRG now or RTOG NRG GOG core committee, he submitted a trial in the setting of intermediate risk I believe where they got definitive therapy, so either they got radiated or they got radical prostatectomy, that they get randomized to get TRT or not. That trial had initial enthusiasm and now it's I would say at best lukewarm. And as we've talked his comment to me is one he has trouble interacting with the appropriate group that would supply the TRT. So maybe I could ask you your advice about if there's an appropriate group that might be interested in this. And then other part is just the interest of getting the cooperative groups to fund that as a priority above other things.

DR. KHERA: The hardest thing to get that study started was FDA approval. It took me 18 months to fight with the FDA back and forth to finally get them to approve. And the part that stuck the most was I do primarily ED and sexual function. That's what I do. And so it's my belief that a hypogonadal man is at a significant disadvantage in recovering in recovering his erectile function compared to a eugonadal man, and he must get that testosterone within the first six months. That's important to me. The FDA did

- not want me to give that testosterone for a year. They said we want to see what happens for a year. I said I won't do the study. And after much debate they let me do it at three months as long as there were two undetectable PSAs. And so now we have an IND that anyone can jump on and use for an FDA-approved trial, but the funding and getting the placebo is a little tricky.
- DR. FINKELSTEIN: Right.
- DR. KHERA: And that's the tricky part.
- DR. VESTAL: Well one might say the protective effect would be a better way to go simply because you can probably get funding for the protective effect rather than the sexual function. That actually to me as an oncology guy shows a lot of promise.
- DR. KHERA: Right, which we're looking at MD Anderson right now. We applied for a DOD. We haven't got it but I think in that protective effect we would apply for more government agency funding. That may be a better route to go than try to get industry.
- DR. KREDER: So we've got a couple of questions and I'd like to hear comments. The first question is in the context of the recent FDA committee recommendations how should companies with TRT therapies promote their products in a manner that's ethical and compliant and reflective of the existing science and data?
- DR. KHERA: So I'll tell you what they're doing and what they're doing is they're no longer having commercials saying do you have low energy? Do you have low libido? Do you have ED? If you do get your T checked and you may be a candidate for treatment. And the reason being is because low energy, low libido, and ED are not on the label. It's not an indication. Right? So they can't mention any of the signs and symptoms, even though many of us who treat men with TRT know that it does work but you can't mention it in a commercial or an ad. And they are taking the cardiovascular risk seriously. They are now starting a trial with all, a consortium of all of the pharmaceutical companies mandated by the FDA to start a two-year prospective trial looking at testosterone and cardiovascular risk as well as indications like ED, and it will start most likely in the first quarter of 2016.

DR. KREDER: Okay. Marty, do you have anything to ad?

DR. MINER: No, I agree with Mo completely. It's all advertising has ceased. Actually almost all funding has ceased for testosterone research at this point.

MALE VOICE: Well as a consequence of the publicity with respect to the cardiovascular complications as you know TestroGel, one of the gels is produced by a French company for all of the world, also for the United States and that company went back after, as of 2014 went back and income and revenues were at 50% and they stopped all of their promotion but also, which is for us, for urology or for the medical community they stopped also all of the education programs because we were in Europe extremely, I was extremely involved in educational programs for urologists because urologists don't know anything about it. - - urologists - - when they talk about testosterone they say they don't know, and we were very much involved in the education, worldwide education program outside of the United States from the company with the name of Besins [phonetic] which licensed by the way Androgel to Abbott in the United States. But they stopped all of these activities because of the drop in revenues.

DR. MINER: And it's clear that education is one of the most significant gaps.

MALE VOICE: Absolutely.

DR. MINER: And one of the areas that needs, has the greatest need.

MALE VOICE: We have a debate in Europe in many countries whether it's England where testosterone replacement has been well explored, Germany, also in the Netherlands, a debate with the company whether the industry is where it should be. The general practitioner or the urologist or the endocrinologist or maybe somebody else who is going to be the prime provider of care of man with LOH, and I don't know if you have that discussion here but we were, I'm a strong promoter of having medical specialists and - - urologists in the lead.

DR. MINER: Well that's also a recommendation that anyone who prescribes testosterone should be experienced in prescribing testosterone as well whether they're a primary

care clinician or a urologist. In this country it's not done by a lot of endocrinologists, it's done just by a handful. Most of it falls within urology and the andrologists. But those individuals must be quite experienced.

MALE VOICE: You need a full urological exam.

DR. MINER: Right.

MALE VOICE: Before you start testosterone. How can a GP do that?

DR. MINER: And you need to be able to follow PSAs and--

MALE VOICE: Yeah.

DR. KHERA: So the argument, we talked about this last night, the argument is the urologist should take control of this sector because when it comes to advanced BPH, which patients may have, PSAs may go up, risk for prostate cancer, that's usually going to be a referral anyway. Right? To the urologist and so, and remember that many of the procedures in the U.S. now are procedures for testosterone. We insert a lot of testosterone pellets. Right? That's a procedure that we do quite commonly. Most of the primary care, particularly the endocrinologists don't want to do the procedure. They don't want to do any procedures. They send them off to the urologist anyway.

DR. KREDER: Okay, there's one other question. Are there unmet needs in the area of testosterone replacement therapy? If so, what are they and where should pharma companies focus development efforts?

DR. MINER: There's a great desire to have an oral preparation that can be taken easily without fat and at least at minimum b.i.d. dosing, but ideally once daily. It's probably the thing, the product that's most desired by patients and often asked by patients. Other long-acting forms of testosterone are being sought by patients. Many don't like the idea of having these pellets put in their bum three times a year, or with AVEED it's being met with so-so acceptance because it's in the States it's every ten weeks rather than every three months and it's a large amount of testosterone undecanoate that's given.

DR. KHERA: So we need an oral formulation. And 80% of men who

start a gel today will discontinue the gel by the end of 12 months. Right? So there's a huge discontinuation rate, a huge dissatisfaction with gels.

DR. KREDER: Why do they do that? Why do they stop?

DR. KHERA: So it's a compliance issue. Sometimes they forget to put it on. You know, - - would always teach us if you miss two days of your gel within two weeks you're sub-therapeutic. You know, so you got to really do it every day. And some of them switch over to injections. That's an option but they'll be off the gel at the end of the year. And the other thing is I think in terms of diagnosis we have to increase our understanding of this secondary hypogonadism, obesity and metabolic syndrome, and we used to call it aging. It's really not aging. It's associated with comorbidities and understanding how this plays in and how these patients would be treated because not much is really discussed in this area.

DR. KREDER: So what happens to that patient's testosterone that's on for a year and then stops? What happens to them symptomatically and what happens to them--

DR. KHERA: Sure. So it depends on how long you've been taking testosterone and how high the dose was will dictate the degree of suppression. And most men will recover their testosterone production. You cannot say that they'll recover back to baseline but they'll recover their testosterone production. It typically takes anywhere from six to nine months depending on what they're using. They'll also recover their spermatogenesis as well but not back to baseline, and that also takes about six to nine months.

DR. KREDER: All right, what would you tell a 60-year-old guy that's had two testosterone levels, has the classic symptoms of testosterone deficiency but his levels are low-normal? They're normal but they're at the lower end.

DR. KHERA: Well there's two things I would do. First, I would say what's his free testosterone? Right? Because if his total testosterone is below normal the SHBG goes up as the patients age. At 60 years of age the SHBG is quite elevated, his free T is probably going to be low, and he would be a candidate for testosterone therapy. And in our institution we also check CAG repeats on all patients. We

check the sensitivity, the androgen receptor, and those patients who are more insensitive tend to respond better to testosterone.

DR. KREDER: Suppose his free testosterone is normal but again the lower end of the range?

DR. KHERA: So we should all be clear on how this range came up. It came up in 2006 by the endocrine guidelines who said that the number 300 is the cutoff. And when I asked the chairman and many members on that guideline panel how did you come up with the number 300? The answer I got was we really just picked it. We just felt that men below 300 felt bad and men above 300 felt good. That was the answer I was given. And I said, you know, I said Ron there's a problem here because insurance companies are using this number for coverage.

DR. KREDER: Right.

DR. KHERA: And they got in so much trouble in 2006 that in 2010 when they revised the guidelines they said we're not going to pick a number anymore. The lower range will be whatever your lab's reference range is. So if your lab is 280 to 900 the number is 280. If your lab is 260 to 800 it's 260. And so they don't want to pick a number anymore. So what I'm trying to tell you is the range is arbitrarily chosen. We know that every man has his own set point. Some men feel wonderful at 250, some men feel lousy at 400. And I would argue that it needs to be individualized, not one number fits all.

DR. KREDER: So would you treat that patient?

DR. KHERA: I would. I would give them a three-month trial.

DR. MINER: Well the other thing is you have to really exclude other, say that the main complaint was fatigue then you really need to rule out obstructive sleep apnea or a sleep disorder and improve any underlying comorbidity like that first.

DR. KREDER: So you would treat them for three months with testosterone or with what?

DR. KHERA: I would treat this patient first we'd counsel, we'd look at other comorbidities like we do, we look for thyroid, we look at all of the possibilities. And if he

was symptomatic with a low T, let's say 325 which is considered normal, I would absolutely treat him for three months. At the end of the three months as long as he was compliant I would check his LH and FSH to make sure he was taking the testosterone. If it's not suppressed he was not compliant, and I would ask him how he felt. If he felt no symptomatic improvement I would say maybe something else is going on. But I'd give him a three-month trial.

DR. MINER: Although the gels won't necessarily suppress it.

DR. KHERA: But it will be lower, it will be lower.

DR. MINER: Yeah.

DR. CRAWFORD: So a lot of the studies that people are hanging their hats on were done with IM testosterone. Right?

DR. KHERA: Yes.

DR. CRAWFORD: Which to me, I mean you get that sort of solitude pattern with that, you know, peaks and valleys, and perhaps there are some risks with that.

DR. KHERA: So the biggest risk is erythrocytosis. If you spike the body with testosterone your rate of erythrocytosis in an older male is up to 40%. If you give that older male a gel his rate of erythrocytosis is at about 2%. So we know the spike is pretty detrimental. So we no longer give men one 200-mg injection every two weeks. We don't even give them an injection 100 mg a week. We divide it, 50 mg on Sunday, 50 mg on Thursday because the half life of the drug is eight days. So they get a great baseline with little peaks and troughs and the erythrocytosis comes way down.

DR. KREDER: But even with that.

DR. CRAWFORD: Some people like the, they like the spikes. Don't they feel a little bit high when they get it?

DR. KREDER: But even with that--

DR. KHERA: They do.

MALE VOICE: But there are two issues here. First of all, the gel is the most physiological form of application because you don't have those spikes. However, when you use intramuscular undecanoate one can, I mean like we do in, you have only 750 mg here.

DR. KHERA: Yeah.

MALE VOICE: But if you use, if you have a risk of erythrocytosis and you have 5% of the patients that go far beyond physiological levels of testosterone, although in the 1,000 and so patients that have been treated with Nebido there were no serious side effects, even with those with a very high spike of testosterone. But when you want to apply most physiologically testosterone you have to use a gel or a spray.

MR. MINER: We did a study--

MALE VOICE: Armpit sprays and nasal sprays and all kinds of things as well.

MR. MINER: We did a study with Testopel and found that 39% of our patients exceeded a hematocrit of 52%. So that's a point at which we start phlebotomy or a double red donation. The endocrine guidelines say take action on a hematocrit greater than 54% yet this is all, all of the data that we have about erythropoiesis comes from the polycythemia vera data. So it's all cancer data and it's very different in real world. We don't know if these men behave like polycythemia vera. Erythrocytosis may be the risk of stroke but we don't know that for certain.

DR. KHERA: If you look at men in higher altitudes, say Colorado Springs the rate of erythrocytosis is higher. Right? Just baseline. And you look at men in lower cities like Houston. There's never been a study to show that men who live at higher altitudes with higher hematocrits, have a higher rate of heart attack and stroke than men at lower altitudes, not one. It's a theoretical risk. And the risk really is not the absolute number, it's the rate of rise because if you slowly raise a hematocrit, they did this in mice, up to 90 no problem at all. But if you did it quickly then you get the heart attack or stroke. So it's the rate. It's not the absolute.

MALE VOICE: But in the Tour de France they did it quickly.

DR. KHERA: Yeah.

MALE VOICE: And nobody had a heart attack or a stroke.

DR. KHERA: Yeah, that's right. That's a good point.

DR. MINER: And the other thing is in this country the gels are not, we're having difficulties getting approval now for the topicals and we're resorting more and more to injection therapy. So most of us are doing what Mo is doing, which is using the cypionate in much smaller quantities more frequently to try to achieve more levels of dosing.

DR. KREDER: Why does sleep apnea cause low T?

DR. KHERA: There's two reasons. So when you're hypoxic the main reason is that you get a suppression of LH and FSH secretions, - - in LH and FSH. So low O₂ content inhibits pituitary function.

**Featured Lecture: The Future of Female Urology -
Karl J. Kreder, MD, MBA**

DR. KREDER: Okay. All right, well that was a great discussion. We'll move on now. I'm going to talk about the future of female urology, another area that's got a considerable controversy surrounding it.

So the issues in female urology circle around two particular disease states, stress urinary incontinence and pelvic organ prolapse, and I'm going to discuss these interchangeably because the real question is how you repair these. And the problem is a huge one. Right now there's well over 100,000 sling operation procedures done in the U.S. each year, and in terms of pelvic organ prolapse 11% of women will have surgery for POP some time in their lifetime. So when you do the math and you add these numbers together it's about 400,000 to 500,000 operations a year for these two entities.

We understand the anatomy and we understand what happens here and what causes this. This is basically failure of local tissues and a loss of support because of damage to fascia and muscle. So the questions are how do we repair that?

So up until about 20 years ago these were repaired using the native tissue in the area, anterior colporrhaphy, the Burch, and MMK. The problem with that is you have tissues that have failed and are not the best and you're trying to use them for a repair. So these tended to have high

failure rates. And so over the past 20/25 years we move towards the use of some kind of a graft, and I've listed the different kinds there. There are autologous grafts, so using your own fascia, xenografts or some animal product, cadaveric, and synthetic. And I'll go through these and tell you the advantages and the shortcomings of each.

So this is just a slide showing fascia lata. This is what I used for years and still use. You can also use rectus fascia or a piece of the vaginal wall. And the success rate with these operations is very good. It's 85% or higher. But there is harvest site morbidity and in terms of fascia lata at least some patients have post-op pain in the immediate period. Some people it will last for a while but usually resolves within a few months even in the most symptomatic patients. There were no infectious or thrombotic complications reported in a number of these series. This was my own.

The problem with autologous material is there is this harvest site morbidity and it takes time. So if you look at the studies that compare these autologous grafts to a synthetic graft, which we'll talk about in a minute, it takes probably another 40 minutes or so when you're using a fascial graft and I don't know what your OR charges but ours is like 50/60 bucks a minute. And so when you add the cost of that it can actually pay for the graft itself and then some.

Xenografts have been used in these. The common ones are Pelvicol, which is basically pig skin or intestinal, intestine in the pig, bovine pericardium. The success rates are pretty good. The troublesome thing with these is you can get this foreign body reaction and to get rid of it you have to excise the whole graft. So if you put these in through suprapubic approach you have to go back, do an abdominal incision and excise all of the graft or it will keep recurring. It looks like an area of proud flesh in the vagina.

MALE VOICE: How often does that occur?

DR. KREDER: It's relatively rare, but you know I'd say it's in the 3% range. Okay? And not a ton of these were done. So this is also a pretty hard sell in Iowa where you drive down the road and see these pigs rolling in the mud and

then you're telling a patient I've got just the thing for you, some pig skin. It's sort of a yuck factor associated with it. So that was tried but because of those two things I think lost favor pretty early on.

Allografts were used, cadaveric fascia, primarily fascia lata. There were two issues surrounding the allografts. One was autolysis and the other was the potential for a disease transmission. The first indication that there might be a problem a autolysis came from this article that Mary Pat Fitzgerald published where they had done 67 sacrocolpopexies and about 35 slings and they had 13 patients that had very early recurrences, and they went back on these and they either found a very attenuated graft or absolutely no graft, and the numbers have gone up since this publication. Mary Pat said they've been back on 75% of these patients. And she told me in some of them it looked like they had never had an operation. They couldn't find anything. So there was clearly an indication that it might be a problem here.

And then this article was published soon after. This was using cadaveric fascia lata for sling operations and there were seven very early failures within a month in the autologous group. The comparator group out of 46 they had not had any failures. So autolysis was an issue.

And the other thing was this potential for disease transmission, prion disease transmission. So prion is a protein and there's an abnormal conform that can occur, and there have been multiple cases of Jakob-Creutzfeldt, which is a prion-transmitted disease and you can see them listed here. Mostly there are CNS sorts of things, growth hormone, dura mater grafts. But there's a concern that if you're using a piece of cadaveric fascia in somebody who is in their 40s and has 40 or 45 years of life expectancy you could see some of these. So for those reasons cadaveric fascia went by the wayside.

So then we talked about these biologic options. You can use an absorbable graft which may be slightly better than no graft at all but not much. And there's these synthetic meshes, and there's four different types of these meshes, and pretty quickly we recognize that types 2 to 4 really had very high rates of complications because the pore size allowed for infiltration of bacteria but not macrophages or

white cells. So these were very prone to infection. So generally speaking all of the meshes that are in use today are these type 1 meshes that have very large pore size.

So when you compare, this is a sling comparison, a meta-analysis of a pubovaginal sling versus midurethral slings. The evidence strength is relatively low but it looks like in terms of efficacy there's not a lot of difference between these two. But in terms of perioperative outcomes, so less perioperative morbidity, it seems to favor one of these synthetic meshes.

And then this looks at the efficacy of mesh or graft, these synthetic meshes versus no mesh at all, and these are a number studies here and you can see virtually every single one of them shows a benefit or efficacy in terms of mesh over no mesh.

So sometimes you can just take a look and you can say this probably doesn't look like a good idea, and you can look at the guy on the left and it's pretty obvious that that's not going to end well. And then you look at this intraoperative picture of an anterior posterior mesh repair in a female and I learned how to do these. I went, I did the courses, I went with somebody and they proctored me on their patients, but I never put any in because when I looked at this I just said this is going to be a problem. and the problem I have is I'm going to be the one that has to fix this. There is nobody else I can send these patients to. So I decided I wasn't going to do anything that I couldn't fix myself, and so I never did any of these prolapse mesh repairs.

The complications you see with these procedures are both the same for prolapse and for sling operations. Here you can see a perforation with a placement of a sling in the urethra. You can get extrusion of these meshes into the vagina, erosion into the bladder, and you can get obstruction. Now these are difficult to fix but these are fixable. The biggest problem you get, and the thing that we struggle with all the time, is when patients have pain post-operatively after one of these procedures, dyspareunia primarily. And these are usually temporally related to the mesh placement. It's along the pass of the mesh. You can make it worse when you palpate the mesh. But Jerry Blavias published an article, I think there were about 60 patients

in this series, where he did these salvage procedures in patients with pain, and only about a quarter of the time would pain resolve even with multiple surgeries. So that's a problem when you have a 45-year-old woman who has painful intercourse and there's nothing you can do to fix it. And so when you look at this how often does this occur? Well you see that the pain problem is about 5%, somewhere between 2 and 5% depending on what kind of mesh, but most studies it's about that 5% range. All of the other things there, infectious complications and tape erosion, urethral injury, those are relatively fixable. Pain is the one that we struggle the most with.

And then when you look at vaginal mesh for a prolapse repair again dyspareunia if you look at the bottom across these different products is somewhere in the 2 to 5% range. So when you're talking about 500,000/400,000 operations 2% is not an insignificant number of patients, and these patients are very, very unhappy. So this is the patient that ends up in a lawsuit. And how many have seen the ads, I mean how many have not seen the ads? You must not watch TV because they're all over the place, and when you search for, Google for information on vaginal mesh what pops up are all of these lawyer sites, warning to all women mesh devices have been linked to serious injury and a hotline. And even within our group of physicians that put these in there's a lot of descent and there have been editorial comments made by some very well respected urogynecologists who don't use mesh that really patients can't give informed consent for the use of mesh. And so that sets us up for a major legal issue if you're going to use this. I think you're probably familiar with the FDA black box warning which included both sling mesh and prolapse mesh, and then the subsequent warning which included just mesh for prolapse basically saying the FDA thinks that these have a higher incidence of complications and we're not convinced that they're any better than other standard repair. So it really puts it in a bad light.

So where do we go? I think the answer here is going to be tissue engineering and individualized medicine. It's going to center around a couple of different options either injectable autologous cells, similar to what we do for type 3 incontinence and injectable materials, or it's going to be tissue-engineered grafts for both incontinence and

prolapse that can be a combination of adult stem cells and some matrix or scaffold.

The different types of cells you can use, you can use embryonic stem cells and amniotic stem cells. These are mired in controversy about procurement of fetal tissue and it's sort of come to the fore with the recent Planned Parenthood videos you've seen on TV. What we're using mostly are these adult stem cells and mesenchymal cells usually from a bone marrow or more commonly muscle biopsy. What's been shown in the lab to work are these urine-derived stem cells which come from the kidney which you can obtain with just a urine sample, which makes it really easy to get the cells and then you can stimulate them to differentiate into different types of tissue.

There have been some studies, so these things have been tried in humans. This was the phase I trial, 38 patients injection of stem cells into the urethral sphincter and low and high doses, and it appeared to be safe, and it looked like there was dose response at the higher doses, and this was another study with more patients, and again showed a response at the higher end of dose that was similar to what we are getting with other injectables.

This is a report of five boys mean age 11 years who had a tissue-engineered urethra placed. These were grown on a tubularized polyglycolic acid, which is a Vicryl suture type material, and these have been followed for up to six years and remain functional. And this study recently published in Lancet looked at patients who had congenital absence of the vagina and they had a vagina replaced with a tissue-engineered graft, and follow-up up to eight years showed that the vagina was functional.

So these things have been done. I mean the technology is there. I think what we have to do now is we've got to commercialize the technology. It's got to be more than a one off where you can do it at this center in North Carolina or this center in England but no place else. So we've got to make it a streamlined process, have equipment and kits and sort of things so that it can be done maybe not every hospital but certainly the larger teaching hospitals or large community hospitals, maybe similar to the way we do transplants. You know? Not every hospital does a lung transplant but there's certainly a hospital in

every state that does lung transplants.

So in conclusion, I'd say right now there's no ideal material for use in the treatment of female incontinence and pelvic organ prolapse. Currently I think autologous fascia is probably the best available option but it's limited both in the harvest site morbidity, the time associated with getting it, and the volume that you can get. You can't have all you want. And that tissue engineering I think is going to provide autologous tissue for us with minimal side effects and I think it's going to happen, the question is how quickly this can happen and is there going to be a company that takes this over and gets us to a commercial product.

I've been a consultant for some of these companies and my sense is in my discussions is we're sort of reaching for the stars when we could easily get to Mars. This is not sexy enough. What they really want is they want to grow a kidney, they want to grow a liver, they want to replace an organ. And so in my view I think we've gone beyond what we clearly can do and we're focusing on something that we may be able to do in decades or centuries, but this we could do today if we really focused our efforts.

So I think that's my last slide. I'll stop there and then I'll be happy to take any questions. [Applause].

DR. CRAWFORD: Karl, I've been hearing about this tissue engineering stuff for a long time. Atala was on 60 minutes I think years ago talking about. But where's the beef? As they used to say. I mean there's nothing happening that I know about. I mean you just said oh yeah we can do it at special hospitals. Well why isn't it not happening?

DR. KREDER: Well I think there's a couple of, there's patent issues associated with this stuff so you'd have to buy up some of these patents, and a lot of the tissue engineering is being done by more venture capital type things and the venture capitalists are not wowed by this. They're wowed by we're growing a heart or we're growing a liver. And you may be able to do that stuff in an 100% oxygen environment but I have a hard time figuring out how you're going to give that thing a blood supply and all of that. But these things can be done. I mean they've grown, they've grown whole vaginas. Okay? And they work. All we need is a

- piece of one for these repairs. So I think a lot it has to do where the venture capital money goes and it's going to take I think a big company with a lot of wherewithal to be able to sustain this and make this a marketable product. And right now I don't see that.
- DR. CRAWFORD: If there's so much promise in this, I'm not sure I buy this. That there are companies that will pick this up, like the fascia stuff you're talking about or other smaller things. Why are they not doing it? I mean it must not work or something.
- DR. KREDER: I mean these are good papers--
- DR. CRAWFORD: There's a lot of promise--
- DR. KREDER: And talking to the people. I mean I think you've got to believe what's in the literature and it looks like it works. It can be made to work. And these are not just, this is not just out of North Carolina. Some of those injectable cell studies were done at other places. My chancellor's - - .
- DR. CRAWFORD: But I mean they've been talking about making bladders now for, you know, since I was a resident I think. It's been a long time.
- DR. KREDER: Yeah but that's the problem is I think let's make a piece, let's make some bladder mucosa, you know? Making an orthotropic bladder is a huge jump.
- DR. CRAWFORD: Yeah.
- DR. KREDER: And they've put in these intestinal conduits that were tissue engineered. The problem is the things didn't get enough blood supply and so they tend to scar down. I think you've seen that published data. And so I think that this is all doable it's just going to take the resources behind it to get it done.
- DR. CRAWFORD: So what about PRP, platelet-rich plasma? Any of you guys using that for anything?
- DR. KREDER: Well I know there's a urologist that's using it for ED and injecting it, and the problem is it's all off label so it's all paid for. There's no data other than it works great kind of thing. It's about 2,000 bucks a pop. But I can speak to that personally because I had a tear in my

rectus tendon or whatever and it showed up on MRI and I went to the - - . This was about six years ago. And he said well we can operate on this, open it up, and make an incision, and sew this thing up, and it's six or eight weeks on crutches and blah, blah, blah, or one of my partners is doing this platelet-rich plasma. And at that time this was a pretty innovative thing. The only people that really were having it done were athletes and that kind of thing. So I got it done and it worked. I mean I haven't had a problem since. It's really, really painful because it's the opposite of like a steroid injection.

DR. CRAWFORD: You can't put any anesthesia in with it because it inactivates it.

DR. KREDER: Right. Right and it--

DR. CRAWFORD: Lidocaine or that.

DR. KREDER: Yeah, double martini was the anesthesia of choice.

DR. CRAWFORD: I have, yeah, I had a similar situation from a lot of running and falling and then they told me I needed a right hip done, and this was like two years ago. And I had a steroid injection, ran Boston, did that, and it was like I couldn't even sit in the car, this and that. So I went and this guy did it and I had three injections. It's like a miracle. I mean I don't even know anything is wrong.

DR. KREDER: Yeah. Yeah.

DR. CRAWFORD: And I was due for a total hip last year.

DR. KREDER: So that's anecdotal but it's pretty easy. You sit there, they draw your blood, they put it in this centrifuge, they take it back and they inject it right there.

DR. CRAWFORD: And it hurts like, you're right, it hurts like hell.

DR. KREDER: Oh yeah.

DR. CRAWFORD: To inject your hip they go right anteriorly right through your groin area right into your hip and it hurts man.

DR. KREDER: Yeah, I had it done and then I had to go MC a retirement party for one of my faculty and I could barely

stand up. I mean and then I had a couple of martinis so it was really a struggle to get through that night. Other questions or comments?

DR. VESTAL: Yeah, we use the ACell which is very similar for reconstruction of the vaginal fistulas, which works really really well but one thing you didn't address is, and Mo I told you I was going to ask you, sexual female dysfunction and whether urology should be involved in female sexual dysfunction just as we are with male sexual dysfunction because of the new drug coming out probably.

DR. KHERA: So I can comment on that. So eight years ago when I started my practice I used to treat a lot of men for ED and we would get them to have these amazing erections, this amazing libido and they'd go home and they'd have no one to have sex is because I mean the reality is their wives were post-menopausal, they hadn't had sex in ten years and many wives would honestly call my office and say look we were fine until he saw you and now we're fighting all the time and he wants to have sex all the time and I don't want to have sex with him and he wants to have sex all the time. and so it was a big problem. And so quickly we realized that you got to treat the partner. And so we treat all the partners, all the wives. We bring them in, we treat them for FSH and Goldstein did a very similar study. It was amazing. If you treat men with Viagra and just give the women an FSFI questionnaire and never meet them as the men's sexual function scores increase the female sexual function scores increase, and it works vice versa. If you give women testosterone, raise their sexual function, guess what? ED scores start to improve with no intervention at all suggesting it's synergistic. And if you're just treating one partner you're missing half the boat. You really need to treat the opposite.

You said something very important. So flibanserin is the first drug on the market that will be voted on by the FDA on August 19th, next week. So right now we have 26 drugs for men, we have 0 for women for sexual dysfunction. And the advisory board, the FDA is voting on the 19th to approve this drug. It will be taken daily. It works with neurotransmitters, serotonin, norepinephrine, dopamine, and increases sexual desire in women. They take it every day and it significantly enhances their desire for sex. So we'll see. It's a lot of media that's going to come out

next week.

DR. VESTAL: But should urologists be in charge of that?

DR. KHERA: Absolutely, I think that we treat ED and it's not very difficult to treat FSD, and I think that both the patients and, both the partner and the patient should be treated simultaneously.

DR. KREDER: One more question; the new RF treatments for vaginal rejuvenation, are you aware of those?

DR. FINKELSTEIN: Yeah, I have no experience with them so I don't know. Do you have any--

DR. KREDER: Anyone else?

DR. KHERA: So I've seen the data and the claim is that it improves vaginal tightening, it causes some sclerosis where it will improve incontinence, but I think that more data needs to be out there.

DR. KREDER: Because that was in favor a few years ago and then it sort of dropped off the map.

DR. VESTAL: I mention it because the gynecologists in our area have just taken to this like flies to you know what. But--

DR. KHERA: So there is a financial benefit I'm just going to mention. The machine is like 60,000 and you can charge 2,000 per treatment and so sometimes, I'm just saying that there is a benefit there.

DR. VESTAL: Financially?

DR. KHERA: Yes.

DR. KREDER: Yeah. And the limited data that was out when it was first introduced looked like it was reasonable. It was about like a Burch, at least short term. Any other questions? Yeah?

MALE VOICE: Mention anything about MiniArc slings in terms of pain?

DR. KREDER: Yeah, so MiniArc--

MALE VOICE: Reversibility of it if you did?

DR. KREDER: I think the data suggests and the meta-analysis

suggests that they don't even hold up in terms of efficacy. And so they're much worse in terms of efficacy, and they have the same issues with pain, erosion, and so I think they've really fallen out of favor.

DR. CRAWFORD: All right.

DR. KREDER: Okay, all right.

DR. CRAWFORD: Thanks Karl.

DR. KREDER: Thank you very much.

**Session 7: The Future of Castration-Resistant
Prostate Cancer: Part 2 - E. David Crawford, MD**

**Featured Lecture: Radiopharmaceuticals - Daniel P.
Petrylak, MD**

DR. CRAWFORD: Very good. [Applause]. And so now we're going to move into the final session. Any other questions or anything anybody has? So Dan, we're going to talk about castrate-resistant prostate cancer and a little bit of discussion. Is Gregg Bernier here or not?

MALE VOICE: He is not here.

DR. CRAWFORD: He's gone?

MALE VOICE: Yeah.

DR. CRAWFORD: All right, so we don't have any presentations. All right.

DR. PETRYLAK: So--

DR. CRAWFORD: Dan we have.

DR. PETRYLAK: I guess me. So I was asked to talk on radioisotopes and the treatment of advanced prostate cancer. As we know there are two basic types of particles that are seen in patients with this, or at least treated with isotopes 1 or the alpha particles which consist of basically helium nuclei. They can cause about one to ten DNA hits per to kill a cell. The beta particles require more hits, between 100 and 1,000. They will generally cause single-stranded breaks as opposed to the double-

stranded breaks that we see with alpha particles. And this explains in part some of the differences that we see in the efficacy of these particular agents. Both strontium and samarium were previously approved for men with castration-resistant prostate cancer based upon palliative endpoints. And they relieve bone pain in patients with painful skeletal metastases, but they don't improve survival. And this may be again because of the mechanism of action.

These are some of the trials that have looked at both strontium and samarium in prostate cancer, and we see again there's improvement in pain parameters such as visual analog scores or the subsequent need to administer radiation therapy as demonstrated by author Porter. It was only until a randomized phase II trial was performed by Dr. Nilsson in 2007 that we started seeing an improvement in survival. And again this was with alpha part blockade versus beta blockade.

So just skipping forward. What's some of the other importance characteristics of a patient who may be treated with alpha-emitting particles. Well the radius of treatment is much smaller with an alpha emitter as compared to a beta. We see that from this particle cartoon. And this has important implications for toxicity. There's less marrow that infiltrated by the alpha particle. It's a smaller radius and therefore can target the tumor cell. This tracks in the same area where calcium is present, and again this leads to at least a neighborhood effect as far as tumors are concerned.

Well what's the data that has led to the support of the use of alpha particles in metastatic castrate-resistant disease? This is the ALSYMPCA trial which has been published looking at alphasadin or radium-223 which is an alpha particle in men with castration-resistant prostate cancer. And there were two groups of patients treated on the study, those who were chemotherapy naïve versus those who were experienced with docetaxel, and those patients who entered were stratified based upon this as well as the fact that they may have elevated or alkaline phosphatases, and prior bisphosphonate use.

These patients had to have at least two bone metastases and they were symptomatic. They could not have visceral disease.

These were the endpoints, the primary endpoint is overall survival, and then the secondary endpoints were time to the occurrence of the first skeletal-related event, time to total alkaline phosphatase progression, alkaline phosphatase response, normalization, as well as time to PSA progression safety and quality of life. Again, these are the same criteria that I mentioned a moment ago.

THE patients were well balanced in terms of age, ethnic background, extent of disease. As we see there were about 41% of patients had more than 20 bone metastases in this particular study. Hemoglobin, albumin, total alkaline phosphatase, LDH, PSA, these were all well balanced, and about half of patients had bisphosphonate use. Overall about half of patients had prior docetaxel use in this trial.

So this is the survival curve that's been presented. There's an overall 3.6 month difference in overall survival for those patients who received six treatments of radium-223 versus those patients who were in the best supportive care alone arm. And this was significant. And when we start dividing this up based upon prior chemotherapy there is a greater benefit in the pre-chemotherapy patients. It's a 4.6-month difference in median survival versus about a 3.1 difference in median survival for those patients who are post chemotherapy.

Most importantly when we start looking at time to first skeletal-related event this is also significantly better in those patients who receive radium versus those who did not. It's about a six-month difference in the time to that event in favor of radium-223.

Now if you start breaking up these particular components in terms of different factors that lead to the composite endpoint this is really the first time that we've seen improvements in spinal cord compression and this is actually something that has not been reported with any other agent.

Safety data, this was well tolerated. In fact, if we start looking at discontinuation due to adverse events it's slightly higher in the placebo arm. It's also slightly higher as far as deaths related to adverse events are concerned with the placebo arm as well. Overall there was

a median of six cycles administered in the treatment arm versus five in the placebo arm, and 63% of patients received all of the injections.

Predominantly as far as the grade 3 and 4 side effects are concerned if you look at radium-223 there's a higher rate of thrombocytopenia, neutropenia is about the same, and that again has important implications as far as chemotherapy is concerned later on.

At this time I'm going to go ahead and talk a little bit about how this has implications on sequencing. In patients who were treated with radium-223 there has been a retrospective analysis performed on the effective chemotherapy and the effective radium on the rates of neutropenia, and neutropenic fevers.

So this is a retrospective analysis from ALSYMPCA where 90 of the 615 patients in the radium arm and 54 of the 307 patients in the placebo group subsequently received chemotherapy. And this included patients who received docetaxel, mitoxantrone, as well as cyclophosphamide.

If you look at the patient characteristics from the subgroup analysis it's well balanced, again as far as alkaline phosphatase, bisphosphonate, and ECOG performance status. Most importantly when we start looking at the parameters of those who did not receive radium versus those who did in terms of platelet counts and hemoglobin they seem to be very, very similar in those patients who subsequently receive chemotherapy. And then if we look at neutrophil counts that does appear to be a little bit lower in those patients who receive radium, but that does not translate into significant differences in neutropenic fevers. So I think one of the myths about giving chemotherapy after radium administration is in part dispelled by this. But we clearly need some perspective data to confirm this.

What about sequencing radium with other agents? Is there data available? Well there's no phase I data that looks at radium combined with either abiraterone or enzalutamide. We're actually leading a phase II trial that takes men with castration-resistant prostate cancer. They're all pre-chemotherapy patients and randomized to receive radium, or radium plus abiraterone, or radium plus enzalutamide. And

our primary endpoint in this study is to evaluate radiographic progression-free survival, and we're re-evaluating these patients with a variety of different tests including fluoride PET and MRI after their third cycle to see how this changes and if there is a difference or an interaction between these drugs.

I think it's somewhat more difficult to sequence radium with chemotherapy, or at least give them concomitantly. And Michael Morris has really led the way in this particular field. He's given different doses of radium as well as docetaxel to patients with castrate-resistant disease. And what he's actually had to do is he's had to reduce the dose of radium and also reduce the dose of docetaxel, so this could safely be administered. And what's gone forth has been a randomized phase II trial, and what's in cohort three, which looked at 50 KBq of radium given every other week and then, or for two doses and docetaxel at 60 mg/m², which is lower than the 75 which is currently approved.

They did see febrile neutropenia at the higher dosages in the phase I trial but it didn't seem that this particular randomized trial showed anything significantly better than giving docetaxel alone at the standard dosage. So I think we need to rethink how we're going to sequence this certainly giving them concomitantly has not been shown to be at least more efficacious. I would like to see what some of the results would be with cabazitaxel. I would also like to see how we could potentially administer radium with some of the newer PARP inhibitors which may have DNA damaging or DNA repair effects, and I think that that would be great way to move this drug forward.

There's been some other further updates of skeletal-related events in radium. This was presented at last year's ASCO meeting that when you start looking at the individual components of SSE, as I mentioned before, there does seem to be some improvement in spinal cord compression but there doesn't seem to be any difference in the rate of symptomatic bone fractures or tumor-related orthopedic surgical events. So those are the areas that predominantly drive the SSEs. And then if you're thinking about in terms of overall long-term safety of these patients Nilsson actually updated this at last year's ASCO meeting where he found that there was a very, very low rate of long-term

myelosuppression in these patients. It's less than 3%. But most importantly as our patients are living longer with castration-resistant prostate cancer you're not really seeing myelodysplasia, acute myelogenous leukemia, or any other primary bone cancer. So I think that a lot of the safety issues with radium are being answered on a long-term basis as these patients are being followed.

So in conclusion alpha-emitting isotope therapy improves survival in men with castration-resistant prostate cancer. There's minimal toxicity of this treatment and the important thing in the future is the combination studies with hormones as well as chemotherapeutic agents are currently underway, and I think that will help us better sequence this drug for these patients. Thank you.
[Applause].

DR. KREDER: Discussion? Comments? Do we have any questions, did any come through there?

DR. PETRYLAK: David each discussion, this is about where they can obtain copies. This was, and the second one was about BPH. So nothing at this point that's come through. Yep?

DR. VESTAL: How early do you use this drug?

DR. PETRYLAK: Well, I mean I've used it as early as when I first start them on secondary or these hormonal, next generation hormonal agents.

DR. VESTAL: [Off mic]?

DR. PETRYLAK: So far no problem and I don't expect there to be. And I think that there's been a registry study that's looked at this particular question. It seems to be safe. There actually may be some interaction, in other words a more beneficial effect by giving both at the same time. But that's non-randomized and it's not, you know, it's not being done in a prospective, well it's being done in a prospective fashion but it's non-randomized. So I think that again it can be done. If you look back at the ALSYMPCA trial there are patients who were treated with ketoconazole or other hormonal agents at the same time. So I think it's something that merits consideration.

MALE VOICE: [Off mic].

DR. PETRYLAK: Yeah.

DR. FINKELSTEIN: So coming to you the ALSYMPCA trial was a trial of radium plus best standard of care. That standard of care was circa 2010ish. Right? So all of the things that you currently use were not being used at the time. However, in its current iteration it's still best standard of care. So we see a lot of patients who are given Xtandi, given Zytiga who are administered radium-223. It doesn't preclude you from using external beam, using SBRT, using Zytiga, using Xtandi, in order to give radium. The one thing that can be a problem that I've found is it's kind of hard in my mind to justify Provenge and Xtandi at the same time because you've got minimally symptomatic/asymptomatic and then you have symptomatic. Right? So you've got to be in this like sort of area in between where they have enough disease to be symptomatic but they're not on narcotics. So that's the only thing that sort of is sometimes conflicting when you're going to put in the for the insurance piece of it. But the other drugs most people don't, it's two mechanisms of action.

DR. VESTAL: So that would have been my next question. - - window between symptomatic and barely symptomatic. Would combining Provenge--

DR. FINKELSTEIN: So what I've personally done is so as they come into my decision tree if you're asymptomatic/minimally symptomatic you get Provenge. As Dave likes to allude immunotherapy probably should be used quickly, used first. Right? And get it in. Right? So if you're minimally or asymptomatic boom you get that in and then you can do other things down the line. If you're symptomatic and you're close to being on that narcotic pain medicine use I usually put them in radium, which tends to move, I see a lot of patients who move backwards on the decision tree. They go and are feeling a lot better. They go from symptomatic on narcotics or a little bit of narcotics to no narcotic use. Now they're minimally symptomatic, asymptomatic, and we potentially use Provenge in that situation. If they have missed their window and are able to move the other way.

So I think both of those agents early in the space are very interactive.

DR. VESTAL: Okay.

DR. PETRYLAK: I usually give enzalutamide right after I finish

the Provenge, and that's usually a month. So I mean it's not a huge delay. Generally the question is what's your delay time and development of symptoms. Now enzalutamide is indicated for asymptomatic as well as symptomatic patients, so if the PSA is going up I'll hit them with enzalutamide quickly. So there's no right or wrong way to do this but that's generally the way I go about it.

DR. MINER: Two other thoughts, one is a distinction between narcotics and non-narcotic pain medication I think the insert says that this has to be any kind of pain medicine to give--

MALE VOICE: Right.

DR. MINER: It can't just be - - .

DR. FINKELSTEIN: Yeah, so again from the ALSYMPCA trial only 56% of patients were actually on narcotics. You did not have to be on narcotics to get radium-223. But I think what we see a lot of is people wait until they're on narcotics before they give this. Right? And that's probably too late. It's later than what was actually seen in ALSYMPCA, and those patients in ALSYMPCA were pretty sick. When you look at their inclusion criteria it was technetium-99 positive bone scans with greater than six sites of disease in over 80% of patients.

DR. CRAWFORD: I don't agree, I don't know that they were, I helped design the ALSYMPCA trial and I think I know it pretty well. But I don't think that to say these people were pretty sick. I mean they had a good performance status most of the time that people were on the trial.

The issue was, you're right, is that this drug is sort of getting put in this bucket that when you're circling the drain you use it, and that's because of the baggage that was brought in with strontium, samarium, radioactive phosphorus, everything else we use. And when this trial was designed I thought I don't know what you guys are smoking if you really think that this is going to improve survival rate, and when it did I was shocked. I mean I really, I didn't think it was going to happen. But in retrospect it was a good trial. And the other thing they did that was unique was they didn't go after skeletal-related events, they didn't do set bone scans and things. You did it when needed, and so they had the symptomatic

skeletal events. And half of the people, not quite half, were pre-chemo and half were post-chemo. Right? And actually if you look at outcomes the people pre-chemo did better whether that's, and you know and less toxicity, whether that's lead time bias and everything else I don't know. But I think that the biggest challenge is that this thing has gotten pigeonholed and to post-chemo circling the drain with pain. You're not supposed to have a lot of lymph node disease or solid organ like liver and things like that.

MALE VOICE: Right, right.

DR. CRAWFORD: And then the thing about pain is Lenny Gamelodis [phonetic] because we had a little thing we talked about this, is that almost, he just sent this around, just about everybody has pain. You know? Everybody sitting at this table probably has some pain or this or that or my shoulder hurts. So that's sort of subjective. And I think that the data with this drug are the same as with Provenge, getting it in early sometimes as you alluded to is the right thing to do. But it does help people circling the drain, there's no question that it did, but the problem is a lot of them didn't get their six doses in. So it's a good drug.

Okay so why isn't it just going gangbusters? Let's discuss that. Why isn't Provenge going gangbusters? And I'll tell you why. I know, I think I know why but what, Cliff, what?

DR. VESTAL: [Off mic] - - .

DR. CRAWFORD: Huh?

DR. VESTAL: [Off mic] - - . The other thought, and since you designed the trial, since you designed the trial what do you think about, you know, we all rest our, the drug on survival benefit but what about the drug being given early would also help with these skeletal events? Because if you give the drug over a longer period of time certainly you should improve or make the patient less susceptible to some of these fractures and skeletal - - .

DR. CRAWFORD: Well they actually did find that and then there was actually less spinal cord compression too. Not a huge difference but there was a difference, and I would think if you get, and that's a bad event. And so I would think if you got it in earlier that would be the case.

- DR. VESTAL: So that would be an argument for early and longer is to prevent skeletal events as well.
- DR. CRAWFORD: And the question is can you repeat it after six cycles or looking at that? Giving it. I mean I think the perfect place for it is newly diagnosed metastatic disease. I suggested that to the company three years ago and I was kind of laughed at. Well, and I think that those things are happening now.
- DR. PETRYLAK: I think another important point from the skeletal-related event issue is I think a lot of us are really beginning to rethink the need for bisphosphonates as well as the denosumab and the other RANK ligand inhibitors. Specifically from the standpoint that it may be that if you get a really, really good antitumor response you're not going to have a skeletal-related event be as contributive to the mortality. And the question really is how do we sort this out at this point? I mean this is a good drug. It helps improve survival. It does cause cell death within these metastases but do you really need the bisphosphonates at this point? And do you need the concomitant toxicity of the bisphosphonates, the osteonecrosis and those issues that go along with it. And that's something that clearly needs to be sorted out over time.
- DR. CRAWFORD: Yeah, I think that, well what the STAMPEDE trial that showed no benefit, the Zometa. Right? At least--
- DR. PETRYLAK: No survival benefit.
- DR. CRAWFORD: Survival benefit.
- DR. PETRYLAK: Progression benefit but they did not look at skeletal-related events as an endpoint.
- DR. CRAWFORD: Yeah.
- MALE VOICE: Is anyone looking at patients that have soft tissue metastases along with bony metastases and doing combination therapy in that population? Since right now they're not going to be able to get radium-223 if it's not bone only. But theoretically they would get a benefit if you were treat the entire constellation of disease that they have.
- DR. FINKELSTEIN: So there's a caveat to the bone only. So in the original ALSYMPCA trial there was lymph node disease up to a certain amount. On the product label the lymph node

size doesn't matter. On certain other trials, the global trials they do mandate lymph node size. Does yours?

DR. PETRYLAK: Yes.

DR. FINKELSTEIN: Okay. So lymph node size sometimes does, sometimes doesn't depending on the trial, but in commercial use it doesn't. Visceral does, visceral does. And so that's a problem. So if you have a guy with a complete bone predominant picture in one tiny little site we've thought about does it make sense to radiate the spot out of that little liver met or resect it to render him no visceral disease? And that has met controversy. Let's leave it at that. I personally don't think that's going to help very much. Right? But I do think that it does take away their benefit if they can't ever get radium. I mean so that doesn't, to me that doesn't make a lot of sense. So but I think that there's five other steps that need to happen first because people look at that question.

MALE VOICE: [Off mic] So did the FDA give you that because of financial reasons or because of mortality reasons? The visceral issue.

DR. PETRYLAK: That was part of the trial design. So - - is part of the trial design.

MALE VOICE: Well they accepted that, the FDA accepted it as part of your trial. So if you had not put that in there that would not have been an issue.

DR. PETRYLAK: So I'm not quite sure I understand the question but--

MALE VOICE: Why was visceral an exclusion?

DR. PETRYLAK: Well for the ALSYMPCA trial you might imagine they were getting standard of care but because radium goes to the bone the concern was that you wouldn't see a benefit in the extra osseous sites, and so the trial excluded those except for lymph node disease which was not felt to be a significant contributor to mortality in the end point being survival.

When we went to the FDA obviously that was an exclusion criteria in the trial, so that carried over into our label. I think everybody realizes that if you have visceral mets radium by itself is unlikely to offer a survival benefit to

you. You would need some other therapy to control the extra osseous disease, and you know as Dr. Crawford said there have been proposals to look at a combination of say a novel hormone or a chemotherapy plus radium in patients with a combination of bony mets and extra osseous disease. So those studies will be examined and we'll see what the results are.

DR. CRAWFORD: All right. Any other comments? Again, I think that this is a matter of education to urologists and quite honestly, and Dan I know you're not like this but a lot of medical oncologists are not particularly interested in Provenge and they're not particularly interested in radium-223. Why do you think that is? And then I'll tell you why I think that is.

DR. PETRYLAK: I think two reasons; number one, there's been a dark cloud around Provenge because of a lack of understanding. There's a lack of understanding as to how to use it and how to sequence it. I think that those are the two major reasons. I mean I think that we're tending to think too segmentally rather than thinking broadly in this disease. I mean that's the way I would look at it.

DR. CRAWFORD: Yeah. I think it's a whole bunch of things, but it's just like we hear this from medical oncologists well surgeons are surgeons they just like to operate. Well you want to know something? Medical oncologists like to give poisons and they like to give chemotherapy, and you can just see how they have jumped all over the CHARTA data way out of proportion to what it is. I mean and it's very clearly newly diagnosed metastatic disease and it is a huge survival rate I agree. But also since docetaxel came along, and Dan was the person that really was key in getting that to where it is, there have been five new drugs that probably are somewhat more exciting in a way, and I don't think we need to just stop that we have the future, we're talking about the future it's integrating these things earlier too in metastatic disease. And that was sort of the step forward with the IMAAGEN trial and all of these other ones that are moving these newer drugs back closer and closer to the newly diagnosed metastatic disease and biochemical failure. Things like that.

So now, and I see that. I mean it's just that the, and there are not a lot of Dan Petrylaks around. They don't

know all this stuff. The average medical oncologist is basically a family doctor to 160 different tumors. And they don't know it all. There are not that many people that are prostate oriented or GU oriented around the country. I can name most of them. I know most of them. But a lot of them, and I see this with what happens in the community. You disagree or agree?

DR. PETRYLAK: Yeah, I think that there's a lack of education. I mean that's the whole problem. And the question is you've got a busy guy who is taking care of 10 or 15 different solid tumors can they really expect to understand the subtleties of management in this disease? I mean eight or nine months I got a patient referred into me that was for a clinical trial for progression of disease. He had had Provenge, his bone scan showed maybe a little bit of a flare, and his PSA was stable. I mean this patient did not need to change treatment, and it would not have been appropriate to have treated him at that given time. I think that the fact is we need, these people need to be treated by specialists who understand the disease, whether it's the urologist, or oncologist, or radiation oncologist. They need to understand what the different characteristics are in switching treatment, with selecting treatment.

**Featured Lecture: Therapeutics in Advanced
Prostate Cancer: The Role of the Urologist - E.
David Crawford, MD**

DR. CRAWFORD: Okay. All right, so I'm going to finish it up with a couple of minutes on the role of the urologist in advanced prostate cancer. Some of it I already said.

We have Gregg Bernier, is he here? Oh, you're leaving to catch--

MALE VOICE: Yeah, I got to catch a plane. See you everybody.

DR. CRAWFORD: All right, take care. So at any rate this is extracted from a meeting we had a couple of talks that I've done over the past couple of years on how you integrate the urologist into the management of advanced prostate cancer. And I think we have to really as urologists look at this very seriously, the ones that are left here. There are institutions now where it is sort of expected and thought

that the medical oncologists are the ones that are giving hormone therapy. And this is happening at a number of large places like Michigan, Memorial, I think MD Anderson to some degree, and it's happening even in the community and large urology practice groups where they actually have medical oncologists. So if that's what you want that's fine but I think that as far as knowing the disease, caring for the patient, things like that that the urologist has a broader perspective. I see this all the time. the patients go to see a medical oncologist for a second opinion because they're neutral for prostate cancer and particularly localized disease, and they come back with oh yeah I saw so-and-so, he's 55 years old, we talked about options, there's a high incidence of erectile dysfunction and incontinence with surgery and whatever depending on which side of the bed they get up in the morning or radiation is better this, or we think the patient, because they just read something, should get radioactive seed implants. And you go okay. and the next question is what's the volume of the prostate? What do you mean what's the volume of the prostate? The guy's got 110-gm prostate. Did you know that? Did you think that that guy is a good candidate for seeds? I mean we see this all the time where they don't get the whole picture. So I think that urologists are equipped and we need to be-- multidisciplinary approach is excellent. I don't disagree with that. We need that but we also need to man the helm here with all of these new drugs and things that are happening.

As you can see here that prostate disease progression goes through, and this is not drawn to scale, but we have a period where some people fail, not a lot of people fail in actuality, and they undergo ADT, and probably it says pre-metastatic, and I would say prematurely too. We have very little data on using ADT in men who have biochemical failure. We do it. I mean we know that people have rapid doubling times. We know from the Hopkins data Steve Friedland's [phonetic] data on what predicts prostate cancer death is rapid doubling times, early failure, high-grade cancer. So those are the three big things. Yet we have no trials that show that doing anything in this arena really matters. We had some trials like to see if denosumab delayed mets in castrate-resistant disease, and it did, except it didn't get approval. We have no study of

early ADT versus a placebo because PSA is going up and people aren't watching that, they're not, they're letting them go to mets. Probably, you know, again the only study that sort of, that is retrospective is the Hopkins data where they kept patients away from ADT until they had metastatic disease.

So we have this whole arena right here is wide open for discussion yet we do ADT, PSA goes down, people feel better and then they progress from the standpoint they have a secondary rise in their PSA. And so this is M0 CRPC, and here's here we had the RADAR group came in and now they're saying what you should do scanning even with the PSAs less than 2, and these are the indications. What was found was, and this was mentioned yesterday from our IMAAGEN trial where we thought people did not have metastatic disease. When we did a bone scan we found it in 37% of men that we thought didn't have it. So it just brought to the idea that metastatic disease occurs with low PSAs and high PSAs and everything in between. All bets are off when you're on ADT.

And why do we even care? Well we care because that's a seminal event when you have metastatic disease. That's where all these drugs kick in. That's why the pharma companies and everybody is very interested in identifying it early. And studies that we and others have done for instance with sipuleucel-T early actually translated into a huge survival benefit, 13 months versus 4 months. Probably the same thing with radium too. As we get into this and understand this. And what are the all the companies doing? They're moving their drugs, enzalutamide, abiraterone, ARN-509, up, up, up in the cascade here with the hope, and I would support it 100% that we will be able to improve outcome.

I was just reading, I was asked to be part of a trial with patients on active surveillance, giving them enzalutamide for one year. Okay? Versus nothing. Well that's a pretty gutsy study and enzalutamide is not without side effects. But you know what? that's not new because the guy, and I forgot the guy's name in California years ago and used to give ADT for one year to men who had and instead of doing radicals and radiation if you go back to the third VA study, the third VA study years ago one of the arms was estrogens versus placebo for localized disease. Now

localized disease in the VA study era was completely different than it is now. It was based on digital rectal exam and not PSA and acid phosphatase. And actually DES actually delayed progression and looked like it improved survival if you didn't have a cardiovascular event.

So this is all not new but a lot of stuff is happening and here right now and we're sort of going back and reinventing the past, you know, everybody is excited about the CHARTA trial. Well years ago in SWOG we did a trial with Cytosan and 5FUs and things like that that showed some benefit in newly diagnosed metastatic disease. But they weren't powered and didn't have the number of patients in, and you know - - and I have had this ongoing sort of philosophy, newly diagnosed metastatic disease for years. We've been giving chemo with hormone therapy with anti-resorptives and other things like that and you know what? We think it works too. So at any rate we're now, and working together is important but urologists I think need to be aware of all of these new agents that are out there. And I would say with the exception of one agent these are all things that urologists can give. And the one agent is docetaxel and cabazitaxel. Although Cliff Vestal are you still giving that stuff?

DR. VESTAL: What am I giving?

DR. CRAWFORD: Are you still giving docetaxel and cabazitaxel?

DR. VESTAL: No, we hired two medical oncologists--

DR. CRAWFORD: But you used to give a lot of chemotherapy.

DR. VESTAL: Yeah, I did, I did.

DR. CRAWFORD: So you gave it up? Neal Shore [phonetic] is still and some of the large, but you hired two medical oncologists and so that's why you're not doing it. But anyway, so I would say that probably the two drugs that would not be, and docetaxel is not on here and cabazitaxel, the rest of these things are all stuff that urologists can give. And then we have these new things, radium-223. We heard a little bit about some of these things that are out there. One of them is, so far two of them are negative. We're still waiting to hear on Prostavac. So again, a lot of excitement.

And then what I often here is well it's hard to monitor these patients that are on all of these drugs. Well, this is what you're supposed to do with all of the drugs out there. I mean with Lupron you could say the same thing, in the OA charts we use the word Lupron, leuprolide acetate. But we have to do bone health, and we have to, cardiovascular stuff right now. You're supposed to look at glucose and you're supposed to look at T levels. There's monitoring but there's actually more monitoring with that. Casodex not so much, again hepatotoxicity that you saw with flutamide that you're supposed to do it. Zytiga, hepatotoxicity and then the side effect is mineralocorticoid excess.

So you sort of worry about that. But once you, I have a lot of patients on Zytiga. It's not hard. I mean and then we can get away with using 5 mg. You don't need to use 10 of prednisone. It's not that hard to, and Provenge, Provenge is simple. There was this cardiovascular stuff that was out there. Xtandi is simple too. Xtandi is watching for seizures and things like that. now to some degree I guess you still have to worry about hepatotoxicity. Zometa there's a lot of things you have to watch for there, ONJ, renal toxicity. Taxotere is here, and Xgeva is very easy too except for ONJ. So we manage pretty tough stuff in the OR and ICUs and things like that so there's really no reason why we can't do it. And we know that the side effects of all of these drugs. And one of the ones we use are the LHRH agonists every day. And there are a lot of side effects from that. And now there's the cardiovascular stuff and there's acute renal injury and everything else that's out there. Do we want to give that up? Casodex is easy to monitor. The things with Zytiga where we've already covered this so I don't want to belabor it.

These are things that urologists can easily manage, and the other thing is that you can do this shared care thing with family practice/internal medicine group because there are a lot of issues that go on with ADT that they can help with. Matt Rosenberg and I have done a lot in this thing about even with drugs like Zytiga okay I don't want to deal with drawing electrolytes and worrying about potassium. I don't want to worry about fluid overload or I don't want to worry about the hepato stuff. Let the family practice guy, the

shared care thing work together with you on doing this. They do a very good job, and most of the stuff by the way is being done by nurse practitioners right now.

And there's all of these models of care out there. The academic institution, which is completely different policies, the large urology practice groups, and Cliff Vestal is in one of the largest ones. And you have radiation oncologists in your group too or not? You have radiation oncologists, you have medical oncologists, you have pathologists. I mean so you have the whole thing together. So that's one model. And then there's the small private practice groups and there will be fewer and fewer of those. I mean how many, you got three people with you Jim? Two?

JAMES LUGG, MD: Two full time and three part time.

DR. CRAWFORD: And you have nurse practitioners?

DR. LUGG: PA.

DR. CRAWFORD: PA? And how do you handle? Do you use abiraterone?

DR. LUGG: Yes.

DR. CRAWFORD: And how do you handle it?

DR. LUGG: I just monitor it myself.

DR. CRAWFORD: It's not hard is it?

DR. LUGG: It's not.

DR. CRAWFORD: The same thing with enzalutamide, the same thing with radium, and all of these things. It's not that difficult to do and I think that urologists should get involved. And I think that's it. So the shared care is important. Second opinions, working together, it all works great but we need to continue to I think be sort of the doc for these patients with advanced prostate cancer. And Dan was talking about hospice yesterday and end-of-life care and other people were talking about that too. Urologists can do that. It's not, and actually the patients appreciate it, and we do it. They're the one, you know, that have been with these patients for a long time.

So anyway, and then there was, so I'm going to, there was

one question. Is there a role for 5-ARIs in prostate cancer? And I think the answer is yes, that it's called, there are two things, one is step-up therapy which Franz popularized in Europe years ago where, and we've done hundreds of patients and Judd Mow [phonetic] and I published on it, starting out with like biochemical failures, high-risk patients using a drug like flutamide with Proscar, or Casodex with Proscar or something like that at 50 mg. Except I think it's cheating when you use Casodex 50 mg because we were just using one flutamide twice a day 125 mg along with finasteride 5 mg a day twice a day. And Cliff, you were around when we did that with a lot of patients. Well tolerated. The PSA goes down, they don't have any side effects except for breast. They get breast enlargement and tenderness, which is significant in some people. Other than that they're happy. I've had people 10/15 years on that. No hormone therapy, no osteoporosis, and they're on that drug and it's suppressing their PSA, they feel good. Did we really do anything positive? I don't know. You know? I've had people with PSAs of 80, radical prostatectomies, Gleason 8's, out 15 years and when their PSA went up a few years after it we put them on finasteride and flutamide and it worked.

So 5-ARIs and then that DHT is still the most potent androgen and it has been looked at, I keep blanking on, Dr. Bob Leibowitz [phonetic] in California. That's the guy I was thinking about earlier. He has added finasteride or Proscar to the regimen. There's actually a rationale for using Avodart or a dutasteride over Proscar because of the type 1 and type 2 inhibition and type 1 is supposedly more common with prostate cancer than type 2. So that makes sense.

And do I do it in patients? Yeah, they'll be on combined androgen blockade with a 5-ARI. That happens. So I think that this whole thing about the urologist I think they really need to stay on top, it's education too, and it's working together that matters.

All right, any discussion or comments? Cliff?

DR. VESTAL: What kind of pushback do you get from your colleagues from doing the CAB these days because of all of the different--

DR. CRAWFORD: Doing what?

DR. VESTAL: Androgen blockade, continuous androgen blockade with all three drugs.

DR. CRAWFORD: What sort of pushback do I get from who?

DR. VESTAL: With all of the new theories about the mutations and increasing your chance of enzalutamide or one of the other drugs not working by using your bicalutamide or your ARIs upfront?

DR. CRAWFORD: Well I don't think, they can say what they want. I don't think they have any evidence to support that. I mean out of the block with like newly diagnosed metastatic disease that ARB7 mutations are present in 15 to 17% of people. So we had nothing to do with that. I think that when they, they're now starting to look at that and maybe it is more when they've been on an anti-androgen. But I think that the key here is the anti-androgen helps but the key is adequate suppression of testosterone and with an antagonist or an agonist that works. We heard Stuart talking about different T levels and that yesterday with Eligard, and they're not all equal.

And that was sort of tongue and cheek kidding Garnick about his study but when you think about it what happened was Marc Garnick and Mike Laday [phonetic] and a whole bunch of other people years ago did the leuprolide DES study and it was 1 mg subcu of leuprolide versus 3 mg of DES which had never been studied before, and it found that DES was more effective. They didn't have PSA, but it was more toxic. And at the end of the day, which was one year in their mind, the risk and benefits and the FDA back at that time was anxious to have something besides DES and orchiectomy so they approved it. And then so daily subcutaneous leuprolide was around. And Katiana [phonetic] left but he and others were out selling that daily subcutaneous injection. When I came to Denver in '86, '89 actually is when they started, and it didn't catch on. But what made it was the one month. Right? And so people, and actually the first one month was Zoladex, not Lupron but in the U.S. it was leuprolide. One month was launched and then everything broke loose.

How was it approved? It was approved on pharmacology. It was approved on studying 100 patients, showing that

testosterone went down in 90% of them and stayed down. You didn't, nobody's arm fell off or butt when they got injected and abscesses, and so they approved it. And every other LHRH compound has been approved on pharmacology since then. And it was all based on Marc Garnick's very weak study. It wasn't, they're not randomized trials. There was one randomized trial of orchiectomy versus Zoladex with 380 some people on it which showed actually that orchiectomy was a little bit better but everybody said it's pretty much the same. And that was it, that was it. You know that. And so then with the antagonist at least they had to do it against something else. So the agonists have all been based on testosterone lowering.

Well we also, we know that that there's a variation. Stuart pointed out stuff that we've been involved with and others, and Parakino [phonetic] and Marotti [phonetic] and Clots [phonetic]. Now the T levels are important to outcome and when you don't get it to a low level, and that's what it's all about right now with all of these new agents, getting T down as low as you can. So people have bilateral orchiectomies and they have T levels of 30, and so where did it come from? The tumor and the adrenal gland. And also, so it's not just the failure of the agonist but the tumor in the adrenal gland happens too. But lower is better. And I think that if you can add something, circling back to the question, with a 5-alpha reductase inhibitor to lower T is better. So the lower you can get it the better you are. And I think that a lot of the people that responded to abiraterone and enzalutamide initially, this has been not published extensively in my opinion, where patients who did, that weren't totally suppressed. And in fact if you look at 30% of people that have failed orchiectomy, estrogen, Lupron, things like that, but mostly the leuprolide acetate things 30% will respond to secondary treatment, anti-androgens, and things like that. And those are probably people that weren't suppressed initially adequately.

And so I think we've got our, our goal is to get T levels down and keep them down. I'm not worried about them criticizing me for using an anti-androgen. If I do there's a rationale for using it. Almost all of the trials that have been done have used anti-androgens. So at any rate that, there's still a lot going on that we need to look at

and there's a lot of excitement with all of these new drugs. Any other questions or comments? Michael?

MALE VOICE: Nice talk. I think that the initial daily LHRH it was randomized to DES. There was a DES arm.

DR. CRAWFORD: There was?

MALE VOICE: Yeah. I thought you said it didn't. But my question is I like the--

DR. CRAWFORD: Under 99 patients.

MALE VOICE: Yeah, I know. I like the idea of treating your, as you coined it, D1.5 post-radical patient with some form of finasteride or whatever. And it certainly helps PSA patients stress antigen. But how do you, I assume these guys are M0 when you initiate them. Right?

DR. CRAWFORD: Yeah, when they get scanned and--

MALE VOICE: But how do you monitor them? what do you do? Because it's sort of, undoubtedly you're going to delay treatment for progression. Right?

DR. CRAWFORD: Yeah, but when it's, okay so the question is you're suppressing PSA, you're suppressing the tumor, are you doing any good? If you talk to most people that's bullshit. You know?

MALE VOICE: No, no, no, I agree but just what do you do? I mean do you do annual bone, how do you monitor these guys?

DR. CRAWFORD: PSAs.

MALE VOICE: And what do you look for?

DR. CRAWFORD: Well, a lot of them will go down to undetectable, 0.02/0.01.

MALE VOICE: Okay, and then what? But you're not--

DR. CRAWFORD: When they start, if they start rising.

MALE VOICE: Okay so you look at--

DR. CRAWFORD: But then I will, you know what I'll do? Is I'll up the dose of flutamide from one twice a day to two twice a day or I'll switch to Casodex along with that, and I'm suppressing the PSA. The question is am I doing anything

good for these people? Did they really need it? I don't know. It's not a randomized trial.

MALE VOICE: No but if you don't use an LHRH agonist most of them are not going to get to castrate levels of T.

DR. CRAWFORD: No, actually that's the good thing about Proscar and flutamide, their T levels go up. And that's why they get gynecomastia because it's aromatized the estrogens and that causes the gynecomastia.

MALE VOICE: Right but so--

DR. CRAWFORD: And then they don't have erectile dysfunction, osteoporosis, all the other stuff.

MALE VOICE: But your PSA is going to be less informative than if you really, than we see with normal castration. Right? Because they're going to, most of them are going to have--

DR. CRAWFORD: It's more informative. You just said, okay so here's the deal. You just, you said that PSA stands for patients stimulated anxiety. You said something else. But that's what, but you know, you suppress the PSA and they're happy as hell.

MALE VOICE: I know.

DR. CRAWFORD: You know? I had a guy, okay I had a guy from Salt Lake City who had a Gleason 7 positive margins. I think he had seminal vesicle invasion, had a radical at the famous institute there on the hill, and his PSA went up to like 1 or 2 and he went to see, and this was after he had radiation, and they said there's nothing we can do. You're going to die. So I had given a talk in Salt Lake to a group there about Proscar and flutamide and things like that and hormone therapy, and somehow the radiation oncologist there sent this guy to me, to see me. So this is like seven years ago. So I put him on finasteride and flutamide and his PSA went from like 5 to 0.01 and has basically been there for seven years. Happy as hell. No side effects. You know? No erectile dysfunction or anything else like that. Because this guy came and he looked like some bum. He always comes in blue jeans and a t-shirt, and he had this guy with him and I found out the guy was his pilot. And I go okay, so this guy has got something, and then I found out more about the guy, that he

sort of owned the yellow pages in the United States and made a lot of money. But the upshot is, and Wendy will tell you that, by taking care of this guy this guy has given us three million dollars because of Proscar and flutamide, and is probably going to do to more. And the issue is that he's happy as hell, seven years. I mean he comes, his PSA is undetectable, he has no side effects. Could I have given him hormone therapy? Lupron? Could we have watched him? Yeah, but they told him he was going to die.

MALE VOICE: Wow.

MALE VOICE: Yeah, that's very anecdotal.

DR. CRAWFORD: Oh I know. But I like anecdotes that are worth three million dollars. I'll take those every day.

MALE VOICE: That's very selfish.

DR. CRAWFORD: That's okay.

MALE VOICE: Just so you know.

DR. CRAWFORD: It's all about you. Okay.

DR. VESTAL: David? David, I was the one that asked that question because I learned this from you and Dr. Flag [phonetic] several years ago on a consult, and I've been doing that for many years, especially elderly patients, especially patients who don't tolerate LHRH and you go to intermittent therapy. We've all done that. I will use the 5-ARIs and Casodex a lot, and I've got guys their PSA immediately drops in half. But it continues to drop for five and six and seven and eight years. And it's--

MALE VOICE: That's true and--

DR. VESTAL: And I know it's anecdotal but I'm telling you.

MALE VOICE: No, no, I believe what David is saying. I've done the same over the many years that I've treated prostate cancer. Some of those patients are very, very happy with anti-androgens and this is in the framework of what we called 15 years ago the step-up therapy.

DR. VESTAL: Yeah.

MALE VOICE: And those patients are very happy.

DR. VESTAL: And the ones that do get the breast problems, and that's fairly common, I'll drop the 5-ARI and just continue the anti-androgen. These guys are still doing well with low PSAs.

DR. CRAWFORD: All right.

DR. VESTAL: No Lupron.

DR. CRAWFORD: Any other, any other comments? We'll wrap up here with a final couple of words, finish early. We again want to thank all of the people from industry that are here and sponsored it, and the feedback that I've gotten has been tremendous as usual. A lot of people that have never been here before say this is great. Thumbs up for the guy that won all of the golf awards, sure okay. And to think that Marc and David have actually videoed people to get the word out because a lot of folks don't understand how this thing works here, the interaction, and we're just sort of free floating and we talk about a lot of stuff that is educational and spawn a lot of new ideas and so forth.

We will be putting all of this content on grand rounds in urology website. There's content on there from other meetings including Vail and Point/Counterpoint. There will be publishable things that will come out of this, hopefully it gets the support to do it from Grand Rounds in Urology in print and also on the website. We do have, we mentioned, Fernando mentioned his meeting in Jackson Hole which is a great meeting, and we have one in Vail that will be 26 years for that upcoming January 20th through 23rd. Then we also have one in Scottsdale we do which is sort of general urology. A number of people have been there, Karl has been there a bunch of times and that's a good meeting. And then this next year I think we're, everybody loves the Broadmoor. They're great. the Broadmoor loves themselves because they're very expensive. They always told me they got, Caggiano said he got a steak and a glass of wine or something and it was 90 dollars. I think we should open a little restaurant out here on a floating barge in international territory or something and save, but it's a great place. It is. We're looking at probably thinking about doing it in September next year rather than August, which we've done for the past 16 years. The reason sort of being that in fact it may be cheaper if we come here in September and then we don't have all of the, you know

Europeans take off the whole month of August for vacation and maybe some other times they do too. But at any rate it's hard to get them out and so they don't come. So we're thinking maybe if we did it in September we might get, might get them. We're also looking at Cheyenne Mountain which is just down the road. It's a very nice place. It's not the Broadmoor but it's a nice place. It has nice views and all of the other things that you can do there. But we'll see. We haven't totally ruled out going elsewhere. We did go to the Greenbriar once. That was fun but that was hell to get to. It wasn't easy, and that was fun but it was hot. We went to Charleston and we were at the Charleston hotel there. I forgot the name. What was the name of that hotel Mark?

MARK: Charleston Place.

DR. CRAWFORD: Who?

MARK: Charleston Place.

DR. CRAWFORD: Yeah, it was great. It was a good old place but you know what? It was hot in August. You sweat a lot and so we've also, we've also gone to Cordillera. That might be one thing we might want to think about again. It's up in the mountains. It's really nice. How many people have been to Cordillera with us? Yeah. It's a nice place. And we also have done it in Breckenridge and places like that. So there's a lot of other opportunities exist. Most people really like it here. I mean it's hard to beat this place, and hopefully we'll be able to work some financial arrangement out that's reasonable to do it here again. But again we appreciate the support. You'll be hearing from Mark and are we going have stuff on the website? All the slides and everything? Or how is that going to work? What are we going to do?

MARK: Yeah, everybody will get an e-mail of how to get the presentation slides and we'll be transcribing the audiotape and we'll have access to that. And our plan is to put together some of the presentations here for the website as well on the educational side. So if you have any questions you can just e-mail me and then we'll be following up to make sure whether it's a thumb drive or just a downloadable step for all of the educational presentations.

DR. CRAWFORD: Now I mean this for instance, I mean the talks

have been great. the two talks that you guys gave on TRT or whatever you call it now and testosterone were great, were wonderful. I mean people ought to have access to that. You don't get that everywhere. I mean you've got to go to a lot of meetings and chase you guys around to get that condensed view of what you said. It was beautiful. I mean it really was, and our residents ought to be listening to that stuff. They ought to be listening to a lot of things, and the general practitioners. So I'm working on ways to try to get stuff like that out, and education for reps and stuff like that.

So at any rate again I want to thank everybody, Marc and David, Educational Measures back there, you guys thank you. And thank all the staff and everybody at the Broadmoor. So that's it. See you next year. [Applause]. Thank you Steve for coming.

MALE VOICE: Thank you.

[Background conversation]

[END Day 4 Sessions 6 and 7.mp3]