

# **Keynote Luncheon: Overview of Prostate Cancer Treatment Options**

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## **I. Overview**

Prostate cancer is the most common malignancy in either man or woman except for skin cancer. It accounts for 28% of all male cancers, and 32,000 men die of prostate cancer every year, which accounts for 11% of all male cancer deaths second only to lung cancer as the cause of cancer deaths.

## **II. Incidence**

The incidence of prostate cancer in the population from 1975 to about 2007 increased dramatically with the introduction of the PSA test in 1991. As fewer men die of heart disease, stroke and cardiovascular disease, men live longer and longer and then become susceptible to dying of prostate cancer. From 1930 to about 1990 the death rates from prostate cancer were increasing as the population aged, and then with the introduction of the PSA test they leveled off. Since 1995 they dropped faster than for any other cancer, and there's been a 40% decrease in the age-adjusted prostate cancer mortality rate since the beginning of PSA screening. You can see there has also been a decrease in the lung cancer deaths which has come with the increased awareness of the hazards of smoking and a decrease in colon and rectal cancer deaths also, which is with the appreciation of the importance of colonoscopy and screening for colorectal cancer. In the other cancers where we don't have good methods of early detection, the death rates have remained stable.

## **III. Survival Rate**

The relative five-year survival rate underscores the importance of early detection in prostate cancer. If a man has prostate cancer but it is localized or regional and is not spread to distant sites, the relative five-year survival rate is 100%, which means it is the same as someone who doesn't have prostate cancer. If the cancer has metastasized, however, the relative five-year survival rate is only about 30%. If you lump all of the stages together because fortunately we detect most prostate cancers early these days, the survival rate of most men with prostate cancer today is very good.

## **IV. Early Detection**

The name of the game in terms of curing prostate cancer is early detection, and PSA screening saves lives. There are now data from three prospective, randomized screening and early detection saves lives. In the European trial, as we saw earlier, men who were

actually screened had a 27% lower death rate with ten years of follow up. The mortality benefit was largely observed in the older men, as you would expect.

A really nice trial was done in Sweden with 14 years of follow up, and they showed a 41% decrease in advanced disease, 66% in men who were actually screened and again a 44% decrease in death rate and 56% in men actually screened. If you detect prostate cancer early, you can cut the prostate cancer death rate by almost 50%.

## **V. Active Surveillance**

Active surveillance is an area in which I disagree with a lot of what has been said and what has been published, but let me begin by saying that I have a very large practice that is limited to prostate cancer patients. I do treat many patients with active surveillance, but in general they are elderly patients who have a limited life expectancy. I do not think that active surveillance is something that should be done with young patients.

The rationale for active surveillance is that prostate cancer is generally regarded as a slowly-growing tumor so perhaps it is okay to simply watch patients for a while, and maybe you can do this and still retain the option of treating them if the tumor shows signs of progression either by a rise in PSA or repeat biopsy showing there is more cancer than you thought or that the cancer is a higher-grade, more dangerous-looking cancer than you thought. The caveat to this rationale, however, is first of all in a biopsy in which you take 12, 15, 18 or even 20 snippets from the prostate, there is a huge rate of sampling errors. The other thing is that cancers can acquire genetic mutations over time and become more aggressive. Generally, if you look at active surveillance or watchful waiting studies, in the short-term the results are great, but the farther out you go there are marked increases in cancer progression and death rates with long-term follow up. The reason problem is that no matter what active surveillance study you look at it, if there is any follow up at all every single one of them shows that there are some cancers that have been underestimated, either under graded or under staged. In a sense, there are some patients in all active surveillance populations who came into the study with a curable cancer, slipped through the cracks, and ended up dying unnecessarily of prostate cancer. I think we will see more of this as time goes on and as younger patients are being treated.

One of the problems with the biopsies being inaccurate is if you biopsy a man and he has 10 out of 12 cores that show cancer and it is all Gleason 8, there is no problem with saying it is an aggressive prostate cancer. You will be accurate 100% of the time, but the inaccuracy comes when you say this man has a harmless cancer. If he has a low Gleason grade and a small amount of cancer on the biopsies, and you say this man has a harmless cancer and doesn't really need to be treated, that would be correct only 66% of the time. One-third of the time you would be wrong because if you removed the prostate you would find that it contained tumors with higher-risk features.

## **VI. Imaging Studies**

The imaging is getting better, but it still has a long way to go. In a study of 96 patients all of whom were considered to have low-risk cancers but elected to have surgery, a quarter of them had high Gleason grade prostate cancer or cancer that had already spread beyond the prostate, but the dispensing MRI scans did not detect them. According to the NCCN

guidelines, the timing and value of imaging studies in active surveillance has not been determined, and one cannot rely on MRI scans to see if a tumor is progressing when a patient is on active surveillance.

The risk of active surveillance is that a patient has to get biopsied every year or two years. Infections, bleeding and urinary difficulties can occur with the biopsies, and in recent years with the development of antibiotic-resistant bacteria, we have seen patients who came in for a prostate biopsy and ended up in the ICU for month almost dying of sepsis from prostate cancer. It's not a trivial thing to do a biopsy every two years. The other problem that has been demonstrated by the people at Johns Hopkins, after man has had three biopsies, the rate of erectile dysfunction increases. Patients on the active surveillance studies also have a lot of anxiety about living with untreated prostate cancer, and most of them tend to hang out on the internet reading all of the confusing information and getting more and more upset. Many of them don't comply with the protocol, and a year or two goes by. It's time for their biopsy, and they just skip it. They don't come back for three or four years, and by that time their PSA is higher and their cancer is worse. Another issue is there could be a patient whose cancer could have been completely cured simply by a radical prostatectomy. He went on active surveillance, and now his cancer has progressed. A radical prostatectomy will no longer be enough to cure it. He will need a radical prostatectomy and post-operative radiation therapy in addition to possibly post-operative hormone therapy. There is no guarantee that a patient will be able to be cured if the cancer progresses. For some patients in any active surveillance program, the active surveillance really amounts to delayed treatment of a cancer, which is never a good idea. Repeated biopsies can also cause scarring around the prostate, which makes it more difficult to do a nice clean nerve-sparing prostatectomy if a patient requires it.

The University of Toronto is very pleased that in their study on active surveillance of the patients they have put on the study 60% of them have been able to remain on the study for as long as they followed them, but if you ask them what happened to the other 40% who came off of the active surveillance protocol and had to be treated by surgery or by radiation therapy, half of them failed treatment so they really were unable to salvage 50% of the patients. They are just beginning to see prostate cancer deaths, and I think they are going to see more as time goes on.

Early treatment of prostate cancer has real advantages for the patient. They are more likely to be cured, they are more likely to have fewer side effects, and they are less likely to require multiple forms of treatment to control their cancer.

My conclusion is active surveillance is a reasonable option in men who have limited life expectancy but should be considered an investigational treatment in men who have over a ten-year life expectancy. According to the actuarial tables today, a man who is age 73 and otherwise healthy has a ten-year life expectancy.

## **VII. Surgical Approaches to Prostatectomy**

With regard to the surgical approaches to prostatectomy, which is the best approach, open prostatectomy or the da Vinci robotic prostatectomy? I am in the minority of practicing surgeons who would say that the open surgery is far better.

First of all, the robot was approved in the year 2000, and it wasn't widely used until 2002. We have no data on the ten-year survival with robotic prostatectomy because it hasn't been around long enough. With the open prostatectomy, however, there are good long-term results. I have done 5,600 open prostatectomies, and the incontinence rates at various ages are very good as are the impotence rates. The cure rates of all-comers who were candidates for surgery is about 80%, and of the 20% who failed their radical prostatectomy, we were able to salvage almost all of them with either radiation or hormone therapy so that they did not die of prostate cancer within ten years of the time that they were diagnosed and treated.

One of the big success stories with robotic prostatectomy has been the marketing. It has been spectacular, but if you sit down and look at the data many of their claims don't hold up. The other thing that the company does every year is to estimate what percentage of prostatectomies are done robotically, and the latest estimates are that next year 70% of radical prostatectomies will be performed robotically. When next year comes, that doesn't hold up either. In the State of Florida, 4,500 radical prostatectomies were performed in 2008, and 1,100 were robotic. According to an article that came out in 2010 in which they looked at the reports in medical literature on the outcomes of robotic prostatectomy, and they found that 12 robotic surgeons co-authored 72% of the published studies extolling the virtues of the procedure. In a study from Duke University in which they looked at patients who had robotic versus the open prostatectomy, they asked patients if they regretted the decision to have a robotic prostatectomy. Four-fold more regretted that they picked the robotic prostatectomy, and when asked why they said that they sort of felt like they had been sold a bill of goods. It didn't work out the way they expected.

It is very often said that patients recover quicker when utilizing the robotic prostatectomy, but actually in a prospective, randomized study from the University of Michigan in which they looked at patients prospectively who had the open versus the robotic prostatectomy, the results indicated that both robotic and conventional radical prostatectomy provided comparable short-term, post-discharge recovery including time to normal and full activity, time to driving and the amount of pain medicine patients used. With regard to the claim that there is less bleeding with robotic prostatectomy, with good surgical technique there should be no difference in the percentage of patients requiring transfusion. In an important study from Harvard University, they looked at 950 cases reported by two expert surgeons, one robotic surgeon and the other an open surgeon. They looked at how likely the patients were to have positive surgical margins when they attempted to do nerve-sparing surgery. With the open it was 7.6%, and with the robotic it was 13.5% that had bad margins.

In terms of the cosmetics of the procedure, with the robotic surgery the patient gets five one-inch incisions to put the robotic arms in, and one two-inch incision to pull out the prostate. With the open prostatectomy, there is one incision that is made that is four and a half to five inches. The cosmetics are really not that much of an issue.

The biggest problem with robotic surgery is there is no feedback. The surgeon can't feel anything and can't tell whether the tissue is hard or soft, can't tell whether they separate easily or with more difficulty. Visual and tactile assessment during open surgery provides valuable information. Across the nation the urological complications that would cause a

patient to return to the emergency room or the hospital were 4% with the robot and 2% for open. Urinary incontinence occurred at a rate of 18% with the robot and 11.5% with the open prostatectomy. Incontinence procedures to correct it occurred 9.5% of the time versus 8.5%. Erectile dysfunction occurred in 33.8% of cases versus 18.2% and requiring another operation like a penile prosthesis for erectile dysfunction 2.8% versus 2.1%. The need for further treatment adjusted for disease severity, the robotic procedure had a greater need for post-operative treatment, a greater need for radiation, and a greater need for hormonal therapy.

The study, however, that should scare anyone who has sense away from the robotic prostatectomy is a study from Harvard University based on a national Medicare database. Looking at what percentage of men required secondary treatment for failure to achieve cancer cure within six months of their operation, with the minimally invasive surgery it was 27.8% versus 9.1% for the open prostatectomy. We don't have long-term results on the robotic prostatectomy, but the short-term results don't look so great.

The most important factor in considering robotic versus open prostatectomy is the skill and experience of the surgeon.

## **VIII. HIFU and Cryoablation**

HIFU stands for high intensity focused ultrasound HIFU heats the prostate tissue up to 100 degrees centigrade, which produces a cavity in the prostate. One of the advantages is the procedure can be repeated. The volume of the prostate is limiting, and the procedure frequently requires a preliminary transurethral resection. I have two studies to show you, one that says it's great, and the other says it's terrible. In a study from France in which they treated 800 patients, their prostate cancer specific survival rate was 99%, and their progression-free survival was 83, 72 and 52 for low, intermediate and high-risk disease. In another study from London, they treated 43 patients. Half of them were treatment failure, and three of these patients developed severe scar tissue blocking urination. Two developed fistulas between the urinary and intestinal tract, and they have completely abandoned the HIFU program because of the complication rates.

In cryoablation, argon is run through hollow needles to freeze the prostate. This is sometimes used to salvage patients who have failed regular therapy, but the initial results have been poor with a high complication rate. By the time you get out to five years, almost half of the patients have failed treatment. One of the real problems in terms of side effects from cryoablation is that almost everybody is impotent after cryoablation of their prostate.

## **IX. Focal Therapy**

Focal therapy is for the man who has been diagnosed with prostate cancer. He is not comfortable with not treating it, but he doesn't really want to have radiation or surgery. With this therapy, you don't remove all of the cancer, you just remove part of it, and then you give a drug to ablate what is left behind.

A problem with focal therapy is there is absolutely no data showing that it works, it has side effects, and if you try it, you can mess things up so that you can't really salvage patients with a radical prostatectomy. It almost always leaves prostate cancer cells behind

in the prostate, and it also leaves “normal” cells behind that can later turn into cancer cells because they are genetically abnormal. Very much like active surveillance, it requires repeated biopsies for monitoring.

The other thing is that 80% of prostate cancers are multiple. If you look at patients who have early prostate cancer, it is very often like someone sprinkled pepper in the prostate. It is not really rational to do a lumpectomy for prostate cancer.

The notion that one can use Proscar or Avodart to suppress residual cancer in the prostate is also fallacious. In a study published in July’s *New England Journal of Medicine*, patients treated with these drugs have a higher risk of having the high-grade Gleason prostate cancer. These drugs are frequently used for treating benign enlargement of the prostate or male pattern baldness in young men, and they have now been shown with long-term use to increase the risk for high-grade prostate cancer.

## **X. Radiation Therapy**

I just want to tell you that radiation therapy although it is very good is not worth it. The problems with radiation therapy are that first of all not all cancer cells are sensitive to the doses of radiation that you can safely give, and in addition you may get what are called geographic misses where the patient gets the treatment but the cancer cells were missed. A big problem with radiation therapy is that most men who have prostate cancer have a diseased. Cells are likely to turn into cancer, and when you treat someone with radiation, if they still have a prostate gland, these cells could later turn into a second prostate cancer, which then you would not re-treat with radiation therapy. Finally, another consideration particularly in young patients is that men who are treated with a high dose of radiation have an increased rate of developing bladder cancer or rectal cancer in the fields of radiation. These tumors are often very aggressive, and they require surgical treatment, which is more difficult in patients who have had radiation therapy.

Looking specifically at brachytherapy, it is what I call an operator-dependent procedure. There are some doctors who simply don’t do it so well, and the seeds are too far apart or even not in the prostate. The patient can fail just because of the technical shortfalls. I am often asked about proton beam radiation therapy, and it is really needed for children who have tumors in the head and neck. It is not needed for prostate cancer. A proton facility costs \$150 to \$200 million to build and a tremendous amount to maintain, and the pediatric tumors that it is needed for are rare and could never pay the overhead expenses of the facilities. It is marketed to breast cancer and prostate cancer in order to support it financially, but there are no major advantages to proton beam over external beam radiation therapy. I have personally had patients pay \$150,000 to \$180,000 out of their pocket for proton beam therapy, and there is no material advantage.

## **XI. Hormonal Treatments**

There is a new hormonal treatment that can be used that will lower testosterone without causing the flare response, but I think there are probably very few indications for using it. It is also more painful for the patients, and they have to be injected every month. I see that it is becoming more popular, but I personally don’t prescribe it for my patients.

The company that developed Abiraterone basically did a study that compared it in patients who had failed chemotherapy, and the main reason they did that was because it was easier to get it approved by the FDA. Abiraterone is a form of hormone therapy, and from my perspective you basically have primary hormonal therapy and secondary hormonal therapy. They are effective, they are well tolerated, and they have few side effects. When a patient fails primary therapy, he should get secondary hormonal therapy. Abiraterone is one of the most effective forms of secondary hormonal therapy, but while a doctor can prescribe it, insurance companies won't pay for it. The doctor is faced with the patient who has failed primary hormone therapy. Then he has to put him on chemotherapy, they have to fail chemotherapy, and then he has to come back for secondary hormonal therapy, which costs \$5,000 to \$6,000 a month if a patient doesn't go through the sequence. There are a lot of very promising drugs in the pipeline that are theoretically going to be better because of the intrinsic advantages of the drug.

Docetaxel is the only drug that has been shown to improve survival in prostate cancer. Cabazitaxel is sort of a son of docetaxel. It has now been approved so you can put a man who needs chemotherapy for prostate cancer and put him on docetaxel. If he fails docetaxel, the patient should go on cabazitaxel. It, however, has a 5% drug-related mortality rate. It is more expensive and more toxic, and the alternative for the patients is if you just give them a chemotherapy vacation and then treat them again with the docetaxel, it is cheaper drug, it has fewer side effects, and at least a quarter of them will have a secondary response to the docetaxel. Studies are being done to see whether the 5% treatment-related mortality is because the dosage was too high. If I were a patient, I would wait until those studies were done.

## **XII. Provenge**

Provenge is the first immunotherapy for prostate cancer, but as was mentioned, there's no way you can tell whether it's working or not. It also costs \$95,000, and I personally wouldn't pay that out of my own pocket for Provenge until some of the issues have been worked out.

## **XIII. Questions**

### **Participant**

Are there any preliminary results from the genetic study regarding the probability of prostate cancer?

### **William Catalona, MD**

We are just getting to the point where there are some genetic tests that can be done so that you can assign probability to patients in relation to the general population. I think in the future we will be combining genetic tests with PSA and other blood tests and markers to assign someone's personal risk for having prostate cancer.

### **Participant**

With regard to Provenge are you waiting for more information that you feel is unclear?

**William Catalona, MD**

That is correct.

**Participant**

Robotic surgeons often say that they can see better with the robotic prostatectomy. What is your response to that?

**William Catalona, MD**

It is a very hard thing to explain to patients, but the way that I explain it is go to the Grand Canyon, stand on the look out and look at the magnificent vista. Robotic surgeons underestimate the magnificence of the human eye. Take the most expensive camera with the greatest telephoto lens you have, and take a picture of what you saw in looking at the Grand Canyon. There is no comparison.

**Participant**

Can you also talk about the learning curve for robotic surgery?

**William Catalona, MD**

I have done between 5,500 and 5,600 radical prostatectomies. One of my patients came in the other day and he said, Dr. Catalona, I heard that you have to do 49 robotic prostatectomies before you are an expert. To me that is laughable. It probably takes hundreds or thousands of cases to really have it mastered.

**Participant**

Is it safe to say that the major consideration in terms of the success of surgery is the experience of the surgeon?

**William Catalona, MD**

It really depends on the surgeon's intrinsic ability, experience and practice.

**Participant**

With some of the new drugs that extend life three or four months, what is the quality of life relative to that?

**William Catalona, MD**

If you had to make a case for Provenge, it is really well tolerated.