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Treatment Options: Brachytherapy/Seed Implant

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I was told that we were going to present advantages and disadvantages of treatment options. Although we tout that we can give radiation after surgery, it has never been shown that if you give surgery plus radiation, that is better than giving full dose radiation upfront, perhaps combined with hormones. That has never been proven in a study; I will show data on that. This will be a challenging talk to give in 15 minutes because some may not fully understand what radiation is about; I will have to give background.

I will talk about epidemiology, then go over the types of radiation as well as the anatomy, discuss some technological advances which are important to show where we are now, and then we will talk about the different risk categories. I talk about prostate cancer in terms of aggressiveness: low risk refers to someone at low risk for distance spread, and high risk refers to someone with a high chance of disease spreading outside the gland. This is important in tailoring our treatment and making recommendations.

I am a data driven person and like to practice evidence based medicine, so I will refer to studies. Many urologists refer to how efficacious radiation is or not, and based on really older studies. You cannot rely on those older studies; we did not go to a high enough dose, so our outcomes were poor. Our technology used very big fields. I will show some data showing higher doses does make a difference in terms of getting better outcomes and less complications. I will show some proton beam data, too. These are randomized trials showing that not using necessarily newer technology but at least using higher doses, outcomes were better. Our outcomes are very comparable to surgery, and one might argue better for certain circumstances. We will talk about low, intermediate, and high risk disease, and we will compare the modalities and quality of life studies, and then I will make some conclusions.

There were about 200,000 cases of prostate cancer in 2009. Prostate cancer is the leading cancer in men, followed next by lung cancer , then colon cancer. There were about 30,000 deaths from prostate cancer, making it the second leading cause of death.

Looking at the types of radiation, there are primarily three forms. First is external beam radiation, with the most commonly used being high energy X-rays to treat cancer, delivered from a machine called a linear accelerator. The radiation comes from the head of the machine here, the patient lies here, and we put them in an immobilization device. It can be used as primary therapy as a curative modality as well as postoperatively. Secondly, brachytherapy is implanting radioactive seeds directly into the gland, which is done in the OR typically with the urologist; those seeds remain permanently. Lastly, proton beam radiation does not use X-rays; properties of proton differ from those of X-rays from the linear accelerator. There are only five institutes in the U.S. which currently have the proton radiation, although more institutes are acquiring this technology. The proton beam is a heavy particle beam which, when it enters the tissue, delivers most of

the dose at a certain depth, and there is no exit dose; proton beam radiation is used mostly in the primary setting, yet it has been used postoperatively, too.

What is dose? Dose is the amount of radiation used to treat the prostate gland. A strict scientific definition is energy per kilogram, or joules per kilogram, but I will be referring to a unit called a gray, or centigray; 100 cGy equals 1 Gy. We give either 180 cGy/day or 200 cGy/day, or 1.8 Gy/day or 2 Gy/day, usually Monday through Friday. And if we give 1.8 Gy/day times 42 treatments, which is typical prostate treatment Monday through Friday, that ends up being 75.6 Gy total. So the total dose, you can see here this ends up being seven-and-a-half weeks of daily treatment Monday through Friday.

Looking at the anatomy, the challenge is we want to treat the prostate, but we have the bladder on top of the prostate and the rectum right behind it. It is unavoidable that we will treat some small volume of rectum and a very small volume of bladder. We have come a long way; we used to plan radiation by getting an X-ray first, and this is an example of an old X-ray machine. We have now evolved to using CT scan to help us plan, which we call 3D planning, and we have evolved further to use a technology, which I will show you briefly here, called intensity modulated radiotherapy, a way of coming in at multiple angles to focus on the prostate and minimize dose to the bladder and rectum. This is an example of the old 2D planning, taking an X-ray from both front and side; we ended up with poor outcomes due to treating big volumes, without being able to take into account the movement of the prostate. Nowadays, we get a CT scan, and on each CT scan image, we contra [phonetic] where the prostate, rectum, and bladder are, we reconstruct these in three dimensions, then we approach from multiple angles so as to minimize dose to the bladder and rectum. We now go to higher doses nowadays, yet our complications are just a fraction of what they once were. This is important to remember when comparing surgery to radiation: are we using old-time radiation or current technology?

Precision-wise, we try to keep to 2 mm or so, using daily imaging. We have the urologists put in four gold nonradioactive seeds into the gland, taking an image at the time of CT scan, and then each day prior to treatment, we take an X-ray as the patient lies on the machine, and we try to line up those seeds. We can overlay X-ray images to ensure the prostate is being treated, and we make usually 3-4 mm shifts to ensure we are on target; usually margins we give around the prostate ranges from 5-8 mm.

This is a quick example of old technology we used to treat, for example, from the front, from the back, from the left and right. We would get a lot of bladder and rectum; we could not go to high doses; and we had fairly high complications. Current technology allows us to come from multiple angles and use small margins; we know where the prostate is each day; we take an X-ray, and so, we get minimal dose to the bladder and rectum. Here is an example of the dose: the color lines, the red is the prostate, the blue is the rectum, and you can see how that dose wraps tightly around the prostate. As you get further away, the dose drops off so that we get minimal dose to the rectum.

Prostate brachytherapy can be used under certain situations. You can treat high risk, but you must give typically half the dose with external, then you can plant the radioactive seeds into the prostate as what we call a boost. There are criteria to help in deciding whether we can treat with prostate brachytherapy; the gland has to be small enough; you

need favorable anatomy meaning the bone cannot be blocking too much of the prostate; ideally, you have not had this kind of transurethral resection of the prostate, and minimum obstructive symptoms beforehand. Here is a template. We put the needle in, this is done in the OR under anesthesia, here is the prostate gland, you put the needle in, then pull the needle out. If you have seeds that are preloaded, you will leave the seeds behind. Here is an example of radioactive seeds: we scanned the patient afterwards; you can see this little bright spot represents the seeds.

Whenever we look at modern radiation studies, they always categorize patients based on risk. When I am seeing a prostate patient, I always go through this risk category with the patient to let them know; it helps us predict outcome and it helps us determine what the treatment recommendations are because not all prostate cancer is the same. A low risk disease will do well; you are going to be cured 90% of the time. If we follow these patients, five years is certainly 90%, but at eight or ten years, it is more like 80%. These are the patients we have to worry about, the ones for which we need better therapies.

Looking further at risk categories, here are a few definitions. I was trained at an NCCN institute; this is the National Comprehensive Cancer Network. The most prominent cancer hospitals in the country are part of this organization. NCCN took basically some of the most prominent world experts in prostate cancer, and for each cancer type, guidelines were put together by experts in the respective areas. They came together to make these guidelines such that we can make recommendations.

This is the NCCN categorization, which was recently changed. Groups include: the very low risk group which is someone with a Gleason six or less, someone in whom you cannot palpate nodules; the low risk group, maybe you can feel a nodule, Gleason score between two and six, and a PSA less than ten; the intermediate risk group where you can feel a fairly large nodule on the gland when you do DRE, or you feel two nodules, or a nodule in each lobe, or a Gleason seven, or a PSA between 10-20; the high risk group in which disease has gone through the capsule, or a Gleason of 8-10, or a PSA of greater than 20; and the newly added very high risk group, patients who have involvement of the seminal vesicles, the little organs which sit on the prostate, or they have involvement of the rectum or bladder.

Thus, it is important to keep in mind what risk category into which one falls. When comparing surgery versus radiation, we must keep in mind that we cannot just lump all these prostate cancers together and say this is one recommendation; each of these risk categories have different recommendations. There is another simplified risk group which I will not go into detail on, but it is developed by a radiation oncologist at Harvard, who breaks down the categorization into three groups.

Here are outcomes from dose escalation trials. These trials tried to show that higher doses are better. This will show what we can achieve with our current technology, this IMRT shown earlier. These outcomes are as good as any surgical data, whether low risk, intermediate or high risk.

Starting with the dose escalation trial, this is a retrospective trial, which is a weaker level of evidence. These studies are not the ones that necessarily set the standards of care. These are the studies where you have half the group getting one dose, the other half

getting another dose; these are the ones that set the standards. It is useful to go through IMRT data from Memorial Sloan-Kettering.

MSK has the longest experience in the U.S. with IMRT. They started in 1996, and they basically dose escalated. They treated 561 patients. One must keep in mind when looking at radiation versus surgery outcomes, our patients are always older, number one; they probably have disease that is understaged, the entire prostate is not removed, a third of the time we may have higher Gleason score and more aggressive disease, so we clinical stage meaning we just have to rely on the biopsy; and while the patients are older with probably more aggressive disease, our outcomes are probably the same if not better than those from surgery. MSK went to 81 Gy and followed patients for a median of seven years. After surgery, PSA drops to zero; with radiation, if you are just receiving radiation, it takes one to two years to reach a low point called the nadir. Also, a patient cannot have three consecutive rises; that is considered failure. People who fail usually do not have clinical disease until about ten years later even after they meet the definition.

This study showed a low risk group, with definition of Gleason six or less, or PSA of ten or less, and they showed the different doses used: 64 Gy, 75 Gy, or 81 Gy. The 81 Gy is the blue, and you can see at five years, they basically almost had 100% of patients that were controlled, and I will go through complications and side effects. So this IMR, coming from multiple angles, is again the technology that we use at Mayo, which is standard therapy at any major cancer center.

Look at their low risk: this is the five-year data; they did report under eight-year data. Intermediate risk, radiation alone, 87% at 81 Gy, so these patients were controlled biochemically, meaning they did not have a rise in the PSA after three consecutive rises in their PSA following treatment; these people are considered successfully treated, at least at five years, and also, the eight-year data which they show are controlled biochemically. Here, the high risk group, which had two components, a Gleason of at least six and PSA of ten or over, were 70%. They only had three patients which had distant disease which went to the bone.

What are the complications for IMRT? We had 1.5% who had rectal bleeding, only seven patients of that 561. Grade two means it is not very bothersome; it does not interfere with the activities of daily living. They don't need any type of intervention. Grade three rectal toxicity means they usually need some kind of procedure because the rectal bleeding cannot be stopped; that is less than 1%. The eight-year probability is 1.6%. Urethral strictures is 3%, so very favorable side effect profile compared to surgery. About 50% of patients had problems with potency after radiation, and I would argue this is probably better than what surgery can achieve on the whole, no second malignancy, but I would argue this is a bit early and this is a theoretical concern. We do have to wait for longer follow-up with this IMRT, but we have old data to show that second malignancy rate is very, very, very, very, very low with prostate, so almost to the point of nonissue.

Loma Linda in California has published the largest series on using proton, and I just put this for comparison's sake. There is absolutely no convincing evidence that proton is superior in terms of controlling cancer or reducing complications. There is no published study that will show it to be superior. What it shows with this large series is that it is

equivalent; it is equal to what we can achieve with IMRT. Every one of my prostate patients, I tell them it is absolutely an option, but there is no way that anyone is going to be able to show you that it is better; it is equivalent. This is what the study demonstrates. This is the largest series with 1200 patients from Loma Linda. You had to have three rises in PSA to meet failure; the follow-up was five years. What was shown at five years, with no subcategorization of patients, was that the group as a whole, 75% were biochemically controlled, and then at the eight-year mark, 73% were biochemically controlled.

Comparing the New York study, IMRT has seven-year follow-up, basically, the biochemical control rate is the same; the group as a whole was 70%. They broke it down into eight-year control for low risk, intermediate, and high risk, 85%, 76%, and 72%. This late rectal toxicity or injury, basically serious ones, is less than 1% for rectal, and for grade three, which is serious, it is only 3%. That compares favorably with really any surgical data out there.

We did some randomized data. This is the kind of study which sets the standards of care: 70 Gy versus 78 Gy. This was done at MD Anderson. They found the patients who would benefit from higher doses in their study was the ones who had PSA greater than ten, so these are patients who were more likely to be biochemically controlled. This is time; this is freedom of failure based on PSA. This is the lower dose here. Freedom from distant metastases, patients who had spread elsewhere, you can see the patients who had the higher dose were controlled, more likely.

Harvard did a study, too, which I will not review it in great detail: 70 Gy versus 79.2 Gy. It kind of showed the same thing: the group as a whole who got the higher dose, 80% of those patients were controlled; that is, their PSA did not rise consecutively three times versus 61%. Then they broke it down into low versus intermediate and high risk groups; all risk groups benefited from giving higher doses. This is important to keep in mind when you are comparing.

Now, we will go through the different risk categories and just show briefly a study or two from each risk category. Low risk groups: this is from NCCN, meaning this is evidence based guidelines. Here you see this is low risk T2A Gleason, less than six, PSA less than ten; this is their recommendations for making decisions. It is not meant to be a cookbook, but this is to give you a sense of what options are available for patients. If you are a low risk patient, if you are going to live less than ten years versus greater than ten years, I use a Social Security life table to predict how long a person will live, but references are provided, but for someone who is going to live less than ten years and has low risk disease, active surveillance makes sense. Their prostate cancer is probably never going to bother them; we are going to overtreat those patients. Those who are going to live greater than ten years who have a low risk disease, active surveillance still can be an option, radiation or brachytherapy, which is the seed, or radical prostatectomy. What you notice about this is the world's experts do not say surgery gets a category one, which is a preferred recommendation, and radiation gets a lesser recommendation; these are all equal options because we don't have outcome data for low risk disease to show that one necessarily is better than the other, quite honestly. I think if you have low risk disease, whether you do radiation with IMRT, or do brachytherapy, or do surgery, you are going to do great. If you have low risk disease, you are going to probably have about a 90%

chance of cure over time at five years, and then at ten years, probably 80%. So these patients, we are not too concerned about.

This is an example: IMRT at five years, almost 100% of their patients with low risk were controlled. Here is some data for brachytherapy for low risk patients, Gleason six or less, PSA; these patients were treated. Basically, 90% of those patients were controlled.

Looking at intermediate risk disease, the options for these people are radiation alone, or radiation plus hormones, and you can use seeds plus external. There is debate right now whether people with intermediate risk disease needs hormones or not. There was a study from Harvard which showed if you gave six months of hormones with radiation, you would have a 10% improvement in cure rate, 88% versus 78%. The problem with the study is they did not go to high enough doses with the radiation alone arm, so this is being repeated in a phase 3 study. Anyway, this is the guideline: intermediate risk, patients who have disease on both lobes, or Gleason seven, or PSA between 10-20, so this is the group we are looking for. If they are going to live less than ten years, they say active surveillance is still fine for these patients, or you can do radiation, and it can be radiation with IMRT or brachytherapy, or radical prostatectomy. Again, they make no differentiation; there is no evidence to show that one is better than the other; they don't put a category one recommendation, which is based on randomized data, that one is a preferred treatment.

Now, if you are going to live greater than ten years, radical prostatectomy is still an option, or radiation. So let me show you the data for intermediate risk; again, I will return to that Memorial Sloan-Kettering, 87% of their patients were controlled at five years. This was a study of six months of hormones for intermediate risk prostate cancer. Patients either got radiation alone or they got radiation plus androgen suppression. That study showed that 88% of patients were alive at five years if you got radiation plus hormones, and 78% if you just got radiation alone. But again, they used low doses of radiation, so some argue if they would have used higher doses, you would not have seen that.

Looking at the high risk disease, radiation, in my opinion, edges out surgery. High risk is disease through the capsule, which is what we call T3A disease, or Gleason 8-10, or PSA greater than 20; these patients, with time, over a ten-year period will easily have a 50% or so risk of spread elsewhere. Here, it reads radiation plus two or three years of hormone therapy: I want to point out category one, that means everyone on that panel said unanimously this is the treatment of choice. Surgery is not the treatment of choice. People do surgery for these high risk patients; I believe they end up leaving disease behind, they have positive margins and so forth, and then you have to give radiation afterwards, and thus you are subjecting patients to two kinds of treatment with both side effects. I tell all my residents in my training program, radiation plus hormones: this is the oral board answer.

The new category of locally advanced is patients who have involvement of the seminal vesicle or growth into the rectum. Radiation plus two to three years of hormone: it is a category one. You only do surgery for very selected patients, those who have basically low volume disease, no fixation. They actually said that you could do hormones alone; I disagree with this comment. We cure more people when we add radiation. In high risk

patients on radiation alone, Memorial Sloan-Kettering showed, at five years, a 70% control rate. This busy table shows all the randomized trials: here, half the patients got radiation alone and half got radiation plus hormones, typically for two to three years. If radiation plus hormone therapy was used for two to three years, cure rates were improved between 10-20%. This European study showed that at five years, 60% of patients were alive versus almost 80% with using three years of hormone.

Can you compare surgery and radiation? It is very difficult. Here is a study out of Cleveland Clinic and Memorial Sloan-Kettering which tried to do compare the two. This shows that if a patient fails surgery, and radiation is then used, patients do not do better; patients were worse off because the men were older, the PSA was higher in the radiation than in the surgery arm, the Gleason scores, they had more favorable Gleason score in the surgery arm versus the radiation arm, and yet, the outcome shows that all modalities are the same except for those who got low dose radiation of less than 72 Gy. Thus, if we do surgery plus radiation, we actually may be subjecting these patients to more complications. Radiation was comparable to surgery, and they had a worse group of patients: the patients were older, they had higher Gleason scores, yet, they showed comparable control rates.

There are numerous studies looking at quality of life. This study looks at seed implant, external radiation surgery, and controls, and shows probably more resulting bothersome urinary and bowel symptoms. Sexual function was about the same for all subjects.

In conclusion, I think that the kind of treatment used and resulting outcomes will depend on the risk factor. For low or intermediate risk, whether undergoing surgery or radiation, the outcomes will be the same, but for a high risk patient, radiation is the treatment of choice.

Dr. Stone

I wish we could have a debate between surgeons versus radiation oncologists. The debate regarding radiation and surgery has been ongoing for 30-40 years. When looking at data, we have to tease through the facts, look at the long-term follow-up of 10-15 years worth of data, the number of patients in a study, and such factors as hormone therapy, and who dropped out.

Dr. Thiel

The radiation oncologists are very smart, but the first thing that you will notice is that they move the target. They say, this is not as good as surgery, so now we have got to increase the dose of treatment. You have to be careful with changing those things. Our surgery has been the same forever; it is an easy attacking point. We are not going to change what we do because we think what we do works. Also, notice that the definitions of failure are different for both options. For surgery, if PSA is not down to zero, that is a failure; for radiation, such a definition is failure on three consecutive accounts. Also, the surgery for high grade disease is different: in my opinion, when you compare surgery to radiation and hormones, you are not comparing apples to apples; hormone therapy is not benign. Lastly, there is no evidence that proton therapy is any better than external beam radiotherapy, but it is costing the system 40% more upon delivery; a big push now for government will be to cut down on some of this expense.

Dr. Ko

I think the biggest challenge for both of us are the very young patients in their 40s who have a life expectancy of 30 years, who have very high PSA, high Gleason score, radiation or surgery is going to help, and there are surgery patients that I think surgical removal of the prostate, reducing the primary source of tumor cells, followed by radiation therapy and intervention of medical oncologists will give that person the best chance at some degree of good quality of life and survival. That is debatable, but I see many young African-Americans for whom neither radiation nor surgery alone will help.

Dr. Thiel

Our Mayo Clinic radiation oncologists understand a lot of the confounding things with radiation, and they can give an honest appraisal to identify who would not be a good candidate for radiation.

Male Participant

I am a survivor and advocate, and too often, I hear men say my clinician says I am too young for a prostate screening. That is wrong: don't ever tell particularly an African-American you are too young.

Dr. Thiel

But I may not know a patient's history, but the reason why screening should not be done on just anybody is because we do not know what the PSA is supposed to be at age 29.

Dr. Stone

Statistically, we rarely see a young man present with symptomatic prostate cancer in their late 20s.

Dr. Thiel

With surgery, a young patient's life is changed. He can recover erections after surgery, but he is not going to be the same.

Male Participant

What is normal PSA? [laughter]

Dr. Stone

That is a can of worms there. [laughter]

Dr. Thiel

At Mayo, we use the age adjusted PSA. As you get older, your prostate gets bigger. As mentioned earlier, BPH causes a rise in PSA. We let an 80-year-old guy float around 6.5 without any concern; for a 50-year-old man, PSA should be under two. Most people are using velocity also: a 40-year-old African-American man with a PSA of 0.6, and the following year PSA is 1.3, it is still low but that patient has something going on. A lot of the prevention trials showed there is no safe PSA. But urologists argue that for a man with PSA of 0.8, even though 10% of these men have prostate cancer, does he really need to be treated right now? This is what we do not know the answer to.

Dr. Stone

Some guys who have been repeatedly biopsied have a PSA hovering around eight; this is their new set point. There is no real normal PSA value.