

Radiation Therapy for Prostate Cancer

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I. 2009 Estimated U.S. Cancer Cases/Deaths

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of death in males so it is a very important cancer. A lot has been mentioned about screening for prostate cancer as well as advanced diseases, and now we are getting to the treatment of low-risk, intermediate-risk and high-risk, non-metastatic patients.

II. Anatomy

The prostate is located deep down in the pelvis inferior to the bladder, and it is a very important area anatomically because of its proximity to the critical structures of the bladder, sphincter, nerves, blood vessels and rectum. As a result, a lot of the therapies that are aimed at ablating or destroying the disease in the prostate have consequences. Prostate cancer can spread once it is detected locally into the different portions of the prostate, into the vesicles, and beyond the prostate regionally into the lymph nodes. It can then go into the distant lymph nodes, into bones and then into what we call visceral metastases like liver and lung. Surgeons and radiation oncologists are very interested in the local extent and regional extent of the disease because that is where we target our treatment.

III. Risk Stratification of Prostate Cancer

T1 is a tumor that is identified by the PSA and a negative examination. T2 is disease with tumors of various dimensions detected in one lobe, more than one lobe or both lobes, and T3 disease is that which extends beyond the prostate into the vesicles. T4 is tumors that invade into adjacent organs.

The goal of risk stratification is to identify low-risk patients and treat them with minimal therapy that will reach the best outcome with minimal toxicities. Then you also identify the intermediate-risk and high-risk patients and increase the intensity of treatment because the risk of disease progression is greater. They are willing to endure more side effects to get to a better outcome, and that is why we risk stratify.

At the present, low-risk patients are categorized as those with T1c to T2a and PSA less than 10 and a Gleason score of less than or equal to six. All three factors have to be present. Intermediate-risk patients are those with higher T stages, T2b or T2c, or a PSA of greater than 10 but less than 20 or a Gleason score of 7. The high-risk patients are those with T3 or T4 disease, or a PSA greater than 20 or a Gleason score of 8 to 10.

IV. Low-Risk Prostate Cancer

The radiation options for low-risk prostate cancer include external beam radiation, typically 39 to 45 sessions for a total dose of anywhere from 70Gy to 80Gy. This can be done with regular x-rays, 3D conformal planning, intensity modulated radiation therapy and protons. The other option is brachytherapy where we insert radioactive seeds into the prostate where the radiation is implanted inside the tumor. You irradiate the tumor from inside. They are both equally effective.

V. Intermediate-Risk Prostate Cancer

For intermediate-risk prostate cancer, the radiation dose remains pretty much the same, and the addition of short-term hormonal therapy is pretty much the standard of care. The other option is external beam radiation therapy for about five weeks followed by brachytherapy as a boost.

VI. Image Guided RT (IGRT)

All modern radiation therapy should be image guided. This means we use image guidance to position the target so that you can deliver the radiation more precisely. You can do that in several ways. One is by instilling fiducial markers within the prostate. The machines are capable of doing a quick scan, and we get a reference image that day of at least three markers. We look at the planning scan and based on the contents of the bladder and the rectum or slight rotation of the patient, there may be some tilt in the target that can be corrected right there before the beam is turned on. IGRT should be the norm in all centers. Coupled with intensity modulation, it becomes the best treatment one could possibly get with radiation therapy.

VII. 3D Conformal Versus IMRT Versus Protons

What essentially happens with IMRT is you reduce the dose to the non-targeted structures whereas with 3D conformal depending on how the beam is oriented, you are going to get a higher dose, which could result in side effects as opposed to a proton beam where you deliver the dose to the target of the radiation. There is the high-dose area, and the dose falls off rapidly when you move away from the target. In theory, the dose to the normal structures beyond the prostate is lower with protons as compared to IMRT and 3D conformal radiation. While the difference between protons and intensity modulated radiation can be substantive on paper, there is some question as to whether that difference is clinically relevant. Studies need to be done.

Some of the problems with protons include the fact that the density of tissue is very important. The beam can fall proximal to the target or beyond the target if the patient is slightly rotated. Positioning is absolutely critical. It is also very expensive.

VIII. Prostate Seed Implantation: Indications, Techniques and Outcomes

We do brachytherapy or seed implantation using a perineal approach. We use a template that is mounted on an ultrasound probe, and we go through the perineum. It is ultrasound-

guided, transperineal, template driven brachytherapy. The seeds are about 5 millimeters in length and about a millimeter in diameter. The seeds are put directly into the prostate, and we do post-implant CT scans to see how the distribution of seeds looks relative to what the plan was. In studies that have compared seeding outcomes with proton outcomes, seeding being the cheapest radiation modality and protons being the most expensive, they are absolutely similar with no advantage to protons. Seeding is here to stay there is no question. Biologically it delivers the higher dose, and the results are excellent. Long-term about 10 to 15% of patients may fail, but cure rates are about 85 to 90%.

With external radiation, studies have shown that when you deliver higher doses of radiation you get better PSA control rate. In the past, we used to deliver a dose of around 6500 to 6800 with 3D conformal radiation, and the dose-limiting toxicity was rectal toxicity in the mid to late 1990s. That was when we got IMRT, and we found out that we could protect the rectum better. Then we started to escalate the dose. We are now at doses of around 7500 to 8000. The question is whether the doses that we deliver today make an impact on the tumor. Studies have shown that higher doses definitely resulted in better PSA control rates in these patients with low and intermediate-risk prostate cancer.

IX. Combined Modality Therapy

Combined modality therapy is used for most cancers today because you want to use less of chemotherapy and less of radiation and by putting them together you get a better outcome. The way they act is very different. The addition of hormone therapy to radiation is a very attractive concept and it is here to stay in every aspect and every state of the disease. Any head-to-head trial of radiation and hormones has been won by the combination of hormones and radiation. Most of us who practice in this field feel strongly that it is a winning combination. Of course, hormone therapy has side effects. A Harvard study showed that adding six months of hormones to radiation therapy improved survival in intermediate-risk and high-risk disease. The question is whether we are willing to make a trade for better outcomes for side effects for a short duration of time. An MD Anderson study looked at higher-dose radiation, and they showed that there was a benefit in intermediate-risk patients for a higher dose of radiation. Since they used 3D conformal radiation to 78Gy, even though there was better PSA control, the rectal toxicity rates were over 30%, which is unacceptable. With IMRT, however, the rectal toxicity rates are about 5%. Certainly, higher-dose radiation is here to stay.

Very recently there was a publication in the *New England Journal of Medicine* on the value of adding hormone therapy for the short-term to radiation therapy. The patients that they entered had T1b to T2b disease with PSAs less than 20. They were given 66Gy radiation therapy with eight months of hormones, and the randomization was this versus 66Gy alone. Over 2,000 patients were randomized, and the study was done in 1994, which is when the doses were higher in those days. The median follow up was about nine years, and the combination won as far as overall survival and disease specific mortality. The metastasis rates were lower. The positive biopsy rates were lower with the combination.

Subset analyses were done, and the results significantly favored the combination as far as biochemical failure at ten years. So it was for the positive biopsy rate, but the disease

mortality and overall survival were similar. If patients fail the treatment, and the disease progresses, the longer one lives afterwards, there is a good chance the patient will die of the disease. Long-term follow up is very important to verify whether the PSA relapse translates into a higher mortality. The higher doses of radiation that I mentioned also did not show any benefit on survival but showed a benefit for PSA control.

X. Radiation-Related Side Effects

Radiation-related side effects have to do with the structures that are proximal to the prostate such as the urinary bladder causing urinary symptoms, rectal problems, diarrhea, some bleeding, impotence, some bone issues though rarely. Most complications are manageable.

XI. Hormone-Related Side effects

Hormone-related side effects are significant, but for short-term therapy hopefully they are bearable to get the better outcome that we see could come of it.

XII. High-Risk Prostate Cancer

Moving on to high-risk prostate cancer, the radiation remains the same. The dose remains the same, but the fields are not the same. In addition, we add hormone therapy for two to three years.

XIII. Rationale for Hormone Therapy (HT) and Radiation Therapy (RT)

The rationale for hormone therapy and radiation is that it is a winning combination. Hormone therapy causes tumor regression by inhibiting DNA synthesis and cell proliferation and by triggering apoptosis. It reduces tumor hypoxia, and there is a synergistic effect in that by improving tumor control in the prostate it down regulates PSA production and most importantly provides a systemic effect that could eliminate micrometastases.

XIV. Lymph Node Irradiation: Lymphatic Drainage from the Prostate Gland

With every monthly journal there is a new way of detecting lymph node metastasis in the pelvis. As a radiation oncologist, it is my task to treat the pelvis and these lymph node thoroughly. With new technologies like IMRT, we are able to dose paint, but we don't know where to paint because we don't know what the distribution of the lymph node metastases are. Are the perirectal nodes involved? In an effort to spare the rectum, you spare some of the radiation to some of the nodes. The whole field is advancing, and we are relying more and more on the diagnostic imaging to help us better the radiation. That coupled with an improvement in technology hopefully will be the way forward.

A study that added three years of hormone therapy to radiation indicated that there was a significant increase in relapse-free and overall survival. It is the standard of care. The

RTOG did a study, however, with two years of hormones, and we tend to go with the two years in the United States.

What about the practice of just doing hormone therapy in locally advanced disease? Unfortunately, many oncologists continue to do this. They just put them on hormone therapy. Imaging as we know today is not the best in prostate cancer, but it is going to improve vastly because how many patients have we seen that are bone scan positive who three months later are full of metastases. The sensitivity is wrong. In a study where hormone therapy was compared to hormone therapy with the addition of radiation therapy in locally advanced prostate cancer, it conclusively showed an improvement in outcomes when you added radiation therapy to hormone therapy for all of the reasons that were mentioned. It contains and controls—very important.

Will six months of hormone therapy be enough in locally advanced prostate cancer compared to three years? The answer is no. You need longer-term hormone therapy in locally advanced disease to get the best outcomes.

XV. Radiation After Radical Prostatectomy

In patients with high-risk tumors after prostatectomy, such as seminal vesicle tumors, extraprostatic extension, lymph node invasion, positive surgical margins, and detectable PSA, these are the ones that would certainly merit consideration of radiation therapy. The practice of radiation after surgery, however, is highly variable. In a lot of institutions it is never done, but at institutions like ours, it is always considered. I think every patient should know that it is an option. We treat the prostate bed, and in high-risk patients we treat the lymph nodes also. Typically, we treat the area behind the pubic symphysis, and there are clips placed that we treat along the vesicles. The dose of radiation that we use is anywhere from 60 to 68Gy as opposed to the 78Gy that we use with the primary prostate. It is a lower dose of radiation, however, there could be side effects because after surgery most of the bladder is in the field. Radiation cystitis can be hard to manage because you can get recurrent bleeding and blood clots in addition to urinary retention requiring catheterization and so on.

Randomized, controlled studies were done, which showed that there was certainly a benefit to adding radiation in high-risk patients after prostatectomy. The PSA control rates were significantly superior compared to prostatectomy alone. However, the SWOG study indicated that when you followed them long-term, the addition of radiation therapy, just radiation therapy showed an improvement in survival. This has really changed the practice, and it just makes sense.

XVI. Emerging Modalities

Stereotactic body radiation therapy means that we are using the technologies that we have today such as the ability to do image-guided radiation therapy to deliver very high doses of radiation, and what we do with stereotactic body radiation is we destroy the tissues completely.

A study was just published using stereotactic body radiation in prostate cancer. The patients were T1 to T2 with a Gleason score of less than or equal to 7 and a PSA of 15 to 20. They were low-risk and intermediate-risk patients. The selection criteria were such

that you don't want patients with urinary problems or rectal problems such as inflammatory bowel disease. You don't want to have previous TURP because you may damage the sphincter, and the plan was to deliver five treatments on alternate days, 1000 units per day for a total of 5,000 units of radiation, 50Gy in five fractions using the technology of stereotactic body radiation. It is obviously very concerning for toxicity, and that is why a study is being done.

It was a dose escalation study. The first time was 9Gy times 5 for 45Gy, 9.5Gy times 5 for 47.5Gy, and finally 10Gy times 5 for 50Gy on alternate days. In a week and a half the treatment is over as opposed to eight weeks, and of course they will be looking at delayed toxicities.

In terms of outcomes, so far no patient has failed, but it is very short follow up, a little less than three years, 47.5 for 18 months and only one year for 50Gy.

Where I get concerned is if you look at the grade-four toxicity in the GI group and you look at the 50Gy arm, there is one patient who already has required a colostomy due to permanent rectal injury. Certainly the other toxicities are well within the range of brachytherapy and things like that. This particular patient was taking immunosuppressive therapy for a kidney transplant and so on, but that isn't really relevant to the point. When you dose escalate to the prostate, you absolutely dose escalate to the front of the rectum. The only surefire way of dose escalating the prostate while protecting the front of the rectum is brachytherapy and not external beam radiation. With brachytherapy we are able to deliver doses of about 14,000, and the front of the rectum gets about 14,000. It is different, however, delivered over the period of a year as opposed to the front of the rectum getting doses of 5,000 in just 5 days. Our bleeding rates from the rectum after brachytherapy are about 2%. In patients who are on blood thinners like Coumadin, in patients with inflammatory bowel disease, and patients who are high risk for rectal bleeding, I prefer using brachytherapy, which delivers a higher dose to the rectum and prostate than external radiation, which delivers a lower dose. The difference is the volume of the rectum that gets the higher dose. It is much less with brachytherapy as opposed to external radiation.

XVII. Radiation for Hormone Refractory Prostate Cancer

Castrate-resistant prostate tumors are exquisitely sensitive to radiation because they are highly undifferentiated tumors. There is significant synergy between radiation and chemotherapy in this disease, and it has yet to be explored.

XVIII. Role of Radiation in Stimulating an Immune Response

The role of radiation in stimulating an immune response is an area of research that we hope to further tap into and study in terms of whether the induction of an immune response from radiation can be further accentuated with the use of Provenge for example.

XIX. Conclusions: Radiation Therapy for Prostate Cancer

For low and intermediate-risk prostate cancer radiation therapy with IMRT, protons or brachytherapy are excellent options. The addition of hormone therapy may significantly improve survival with intermediate risk, and certainly PSA control in low risk.

Stereotactic body radiation therapy is still a work in progress, and I would not put a patient in the study until I am convinced that there is a clear margin of safety. It is the patient's choice to choose between surveillance, surgery, radiation, radiation plus hormone therapy, seeds, and whatever in low-risk patients. In high-risk patients there is really no controversy. It is radiation and two to three years of hormones. The role of chemotherapy in addition to that is being studied. After surgery, high-risk patients should receive radiation therapy in addition to hormone therapy, and in the RTOG study with Casodex and radiation in detectable PSAs of around 1.5 or higher is going to be a positive study with better outcome with the combination. Radiation therapy is the present standard of care. For patients with symptomatic disease, radiation therapy is extremely useful and will significantly alter the patient's quality of life. Finally, radiation is very effective for tumor control in hormone refractory and metastatic prostate cancer; it improves quality of life.

XX. Questions

Participant

How are you going to help patients get more information to make more informed decisions?

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Those of us who are passionate about our field need to think like patients. I talk to a patient like I want my doctor to talk to me when I am a patient. Every doctor should know how to do that. If there are doctors who don't know to do that, it's too late. I don't think it can be taught. Go to another doctor.

Participant

What is the incidence of erectile dysfunction from external beam radiation?

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Fifty percent is the number that we quote for patients who get external beam radiation therapy. After brachytherapy, the erectile dysfunction rates are lower, about 30% to 40%. In about two-thirds of these patients, Viagra and other medications help.