

“WHAT IS IMRT AND WHAT CAN IT DO FOR YOU?”

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INTRODUCTI ON

I am pleased to be with you tonight. We are going to talk about radiation therapy for prostate cancer, and what new technology can offer. The simplified title of my presentation is “What is IMRT and What Can It Do for You?” If you are going to choose radiation therapy for prostate cancer, you need to be aware of the recent innovations.

Intensity modulated radiation therapy (IMRT) might also be more descriptively termed “dynamic adaptive radiotherapy” to make it understandable, but no matter the terminology, it implies movement of multi-leaf collimator leaves during treatment to optimize the treatment. IMRT minimizes hot spots and cold spots, evens out the dose to the target, e.g., the prostate gland, and minimizes the dose to adjacent normal tissues by relying on computer optimization. Thus, IMRT results in a sharper cut-off between the organs we wish to avoid treating and the target organs such as the prostate. Certain organs adjacent to the targeted area are sensitive to radiation and can be easily damaged; other organs are less sensitive. For example, arteries are not very sensitive; the nerves are not terribly sensitive. Even the rectum, which is right next to the prostate, is resistant to a degree, compared to the small bowel. Nevertheless, it can be damaged with a high enough dose. The name of the game is to deliver a high dose to the prostate to kill the tumor while reducing risk to adjacent tissue. So we have to find ways to distinguish the rectum and other organs like the bladder from the targeted prostate. There are ways to improve accuracy. We do it, for example, with improved accuracy in outlining the borders of the prostate on a scan, and where the normal organs are, and using IMRT to perform the treatment is another way to improve the results. If you're going to choose radiation for prostate cancer treatment IMRT is the way to go, and that is why I am here tonight.

As I have already noted, better target definition results in improved tumor control and decreased "toxicity", or side effects. External beam radiation therapy has greatly improved over time to make the following gains: better precision; accuracy in “painting” the target and determining the appropriate dosage; image fusion or "marrying" between the MRI, PET, and diagnostic CT scan; intensity-modulated radiation therapy (IMRT); image-guided radiation therapy (IGRT) that uses imaging techniques to check the patient’s position daily at the time of treatment; smaller “leaf” size; multiple beam angles to spread out the dose; and fractionation or spreading out the treatment over time to protect normal organs without sparing the tumor from damage. So these are ways we use to “tease” the tumor away from the normal organs so we can deliver a high dose to the diseased prostate while minimizing damage to adjacent structures. In short, if we can define where the target is, hold it still or track it as it moves, deliver the dose, and reduce risk to the normal organs, we are getting the job done.

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THE TEAM APPROACH

At the outset, let me describe the team approach commonly employed in a radiation oncology clinic. A patient would have an initial consultation and obtain a treatment recommendation from a doctor—a radiation oncologist. If radiation is an appropriate therapy, and the patient selects it, he would meet a nurse, a patient educator, who would help him understand the radiation process, explain the potential side effects and how to deal with them. A simulation team acquires data for treatment planning: for example, the radiation oncologist will be outlining targets and normal structures on the CT scan obtained at the time of simulation for treatment (scanning with the body in treatment position); dosimetrists will be calculating the dosages much as a pharmacist follows a doctor’s prescription for medications but using radiation doses instead of medication doses; the physicist (staff with advanced training in the measurement of X-rays) will be checking the calculated doses for accuracy and does constant checks on the accuracy of the treatment machine's calibration; and when the patient arrives a week or two later for treatment, the therapists will be placing the patient in the proper position to receive the radiation. There are also tiny tattoos placed at the time of the simulation scan that indicate the center of the radiation field on the patient's skin. So there is a lot that goes on after this first simulation appointment that patients are not usually even aware of - the case it moved from one team to the next, sequentially, from doctor to dosimetrist to doctor to physicist and then to therapists on the appointed day of treatment. The entire simulation procedure, at this first visit after the initial consultation visit, takes a couple of hours to put the patient into a reproducible treatment position, insert a urinary catheter into the bladder, take a CT scan in the treatment position and place three tattoos on the skin in the middle of the treatment area at the end of the simulation process, and finally after the patient is off the scanning table, to give the patient his appointment dates after he indicates the time of day he prefers to receive his daily treatment. The next step is to return on the appointment date to start radiation therapy a week or two later. This is a general description of the treatment planning process, starting with the simulation, for which the patient is present. For the other steps in the treatment planning and verification process after the date of the simulation scan, the patient is patiently waiting at home until the date that treatment is scheduled to begin. Typically treatment then lasts for approximately eight weeks, five days a week, once it actually begins, a week or two after simulation.

(Dr. Wilson then displayed and explained a series of slides demonstrating the improvements over time in determining the precise position of the prostate gland by means of computer-generated imaging techniques; intensity-modulated radiation therapy (IMRT); and image-guided radiation therapy (IGRT) that are the basis for state-of-the art radiation therapy. He presented slides describing the earlier method using the so-called lead block technique for treating prostate, lung, and brain cancers and contrasted it with the newest techniques. He emphasized the need for the radiation to be directed from varying angles in order to spread the dose within the target area. These slides have been placed in a PowerPoint presentation available at <http://www.wramc.com/prostate.ppt> and can be downloaded for review by either PowerPoint or the free PowerPoint viewer available online at <http://www.microsoft.com/Downloads>. The text of this talk, in PDF format, will also be there as <http://www.wramc.com/prostate.pdf>)

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INTENSITY-MODULATED RADIATION THERAPY (IMRT)

Let me get more detailed about intensity-modulated radiation therapy (IMRT). It's fairly new; we began using it at WRAMC in 2003. As noted earlier, it allows us to deliver a higher dose to the prostate without damaging the other organs. The higher dose to the prostate cancer, the higher the chance of cure; the lower the dose, the more likely the chance of some local residual tumor. It's as simple as that. In the past, we used to rely on lead blocks to make the radiation field match the shape of the tumor in order to focus the beam. This resulted in certain hot spots and cold spots within the target area. Instead of cutting large custom blocks from lead we switched to multiple leaf collimators--picture them as little piano keys. Instead of large lead rectangles, we now have many tiny lead rectangles that we can move to obtain the perfect shape we seek that fits the tumor shape from any given angle from which we're aiming. These leaves have sensors and feedback mechanisms to help the computer verify they are in the intended shape. This development made IMRT possible.

(Dr. Wilson then demonstrated the IMRT process by a series of slides. He first showed the older lead block technique, noting its inflexibility, i.e., the blocks cannot be moved during treatment, nor can their shape be changed. He then demonstrated the flexibility provided by the multi-leaf collimators--the piano keys. They move, and have sensors and feedback mechanisms to fit a particular tumor shape. Dr. Wilson showed slides of an actual treatment to illustrate the dosage delivery using both the conventional lead block technique and IMRT and the superior control provided by IMRT. He noted that radiation oncologists are finding that IMRT is providing the control they had hoped for with brachytherapy.)

Now for some quality assurance data. First, we have found that the higher doses permitted by IMRT result in a higher chance of cure. Next, we learned that overall side effects from these higher doses are about the same as pre-IMRT when lower doses were used, with a correspondingly lower chance of cure. In short, IMRT improves cure rate without increased side effects.

IMAGE GUIDED RADIATION THERAPY (IGRT)

Obviously, the position of the patient during radiation therapy is absolutely crucial to the precise delivery of the radiation, and organ movement during therapy is a major concern. We needed an imaging technology to complement IMRT. Image guided radiation therapy (IGRT) is meeting that need. It uses imaging methods such as X-rays, CT scans, and ultrasound to check the patient's position daily during treatment. We used to take an X-ray once a week, relying on skin lines to show the bones to check alignment. Then we would make adjustment as deemed necessary. To compensate for these adjustments, we had to make our targets bigger with all that implies for increased side effects. To capitalize on IMRT, we wanted image guidance on a daily basis, not a weekly basis. And we did not want to rely on the bones for adjustments; we wanted to see the prostate, bladder and the rectum to make sure they are in the right position relative to each other. We bought an ultrasound machine specially designed for radiation therapy to do the daily check. We now have started using these special gold marker seeds called fiducials. These marker seeds are placed in the prostate gland to show us where the prostate is. Now at last we can see the prostate! On a daily basis, we can compare our treatment planning CT scan with the

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X-ray provided by our new ultrasound equipment. We also have, built into the newest treatment machine installed in 2007, the ability to use a CT scan daily to check the prostate position, theoretically even more precise than using the marker seeds to mark the position of the prostate, and we will be implementing this once we have upgraded software that allows us to compare old to new CTs, so technology marches on. In any case, this new image-guided capability (IGRT), because it is used daily and is more accurate than simply trusting skin marks and bony anatomy, allows us to shrink the size of the radiation field to target the tumor more precisely and lessen the exposure of normal tissue. Thus, IGRT is the next innovation after IMRT and enhances IMRT.

BRACHYTHERAPY - INTERNAL VS EXTERNAL RADIATION

Now I want to offer some comments about brachytherapy. IMRT is a form of external beam radiation therapy, or EBRT. Brachytherapy is not delivered from the outside but is internal radiation, coming from the prostate gland itself after seeds are inserted into it using needles inserted through the skin through ultrasound guidance. It gained in popularity because some radiation oncologists were dissatisfied with the external beam techniques in use 15-20 years ago. They sought a way to “wrap” the dose around the prostate without leakage outside of the prostate. That’s called being conformal, i.e., conforming to the shape of the target. So seed implants are very conformal. The idea was perhaps they could get higher doses, and thus better cure rates without more toxicity, by having a steeper fall-off as the dose comes from the inside to outside the gland. And it’s true that at least some parts of the gland get higher doses using seed therapy, although there is a problem with evenness of the dose using this technique and some parts of the gland do not get much higher equivalent doses than with current IMRT techniques. In any case, compared to EBRT, one down side of seed implants is that they tend to produce more intense urinary side effects, at least in the short term, such as urinary burning and frequent nocturnal urinary urges, causing loss of sleep for two or three months. There is also more potential for urinary obstruction after the procedure, potentially requiring insertion of an indwelling catheter for weeks to months, particularly if patients are not chosen carefully to avoid those without already severe urinary blockage symptoms. The other side effects are similar to those associated with EBRT. This slide that illustrates the brachytherapy procedure. The seeds are placed using ultrasound and a preplanned template. We typically place about 120 seeds using about 30 different needles, about four to six seeds per needle. This CAT scan shows the location of the seeds within this patient’s prostate. The idea is to spare the urinary tract and the rectum in order to reduce the risk of urinary and rectal side effects. But it’s a balancing act because the first objective is to destroy the cancer. As with any medical procedure, seed implantation has its advantages and disadvantages compared to EBRT. I’ll mention these comparisons later in my presentation. We are seeing less patient interest in brachytherapy despite some claims for higher potency rates. The jury is still out on that matter. Although we still offer the procedure here at WRAMC, IMRT is giving the kind of results that many hoped brachytherapy would provide.

SELECTING A THERAPY AND MYTHOLOGY

The biggest challenge to the newly diagnosed man is his selection of the appropriate therapy. So I thought you would appreciate a brief discussion of the various options and some of the mythology surrounding the process. Not very long ago, 2002 or so, controversial articles

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appeared regularly in the popular press claiming that watchful waiting had “cure rate” similar to active intervention, so why treat? A study of Connecticut Tumor Registry data on watchful waiting led some to say that certain low-risk men did very well after 15 years—only 23% died of prostate cancer. Could active intervention improve on that? For many years, we really didn’t know. This was the so-called “competing risks” issue. The older the patient, the more likely the existence of co-morbidities affecting him. Some pundits (including yours truly) said no randomized trial of watchful waiting versus active intervention would ever be done. We were wrong! The New England Journal of Medicine subsequently published a Swedish study comparing watchful waiting and active intervention. It showed that eight years after diagnosis, untreated low-risk prostate cancer patients had more metastasis to the bones but an equal number were surviving their cancers; by year ten the researchers began to see a difference in longevity as well. Now we know that active intervention can make a difference. Treatment decisions made at diagnosis by low-risk men (Gleason 6 or lower) will come home to roost about eight to ten years later. One final comment about therapy selection. If the clinical data suggest that a cure is possible and you intend to do something about it, the best time to do it is yesterday, so to speak, because excessive delay may let the cat out of the bag and the patient may become incurable due to spread of cancer distantly to become metastatic disease. Thus, for those who plan any treatment ever I advise them to get treatment now. For these men I am not a fan of watchful waiting. For those who choose watchful waiting due to age or other competing risks of death, I feel that is appropriate as long as they know they are not trying to be cured, simply trying to outwait the cancer.

Cure Rate. Cure rate comparisons among the primary therapies always generate interest. It is difficult to compare radiation and surgery as far as the cure rates are concerned because they are both moving targets. It takes 10 or 15 years, if not longer, to get reliable statistics on prostate cancer. So we often found ourselves comparing 20-year-old radiation outcomes with 20-year-old surgical outcomes and by that time the technology has moved far ahead of the old technology, both for surgery and radiation therapy. Therefore, insofar as we can ascertain, EBRT, brachytherapy, and surgery are all equally effective in curing low-risk patients (Gleason 6, PSA 5). For higher risk patients (Gleason 7 or above and a PSA of a least 7.5), we find that adding hormones before and during radiation improves the apparent cure rate, particularly if we treat the lymph nodes and the pelvis. (The issue of treating the lymph nodes has become a hot controversy in late 2007 and people are no longer as sure as they once were.) Higher-risk patients selecting surgery have a fairly high likelihood of needing radiation afterwards because not all of the tumor is removed. (I.e., surgical margins end up being positive for tumor.)

Side Effects. Side effects fall in two categories: temporary side effects and permanent side effects. Comparing EBRT with brachytherapy, brachytherapy has more intense temporary side effects, such as urinary discomfort and soreness in the perineum area; otherwise the side effect profile of EBRT and brachytherapy are similar both in the short term and permanently. (The problem with comparing the side effects of brachytherapy is that it is very operator dependent - in the some hands of some implanters rectal side effects may be lower than with EBRT, but those with little experience may produce side effects much worse than that of EBRT, including IMRT. It is easier to standardize results of IMRT because there is not such a steep learning curve to the technique.)

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When comparing either form of radiation with surgery, the most prominent permanent side effect of radiation is a very small percentage (1-2%) of patients developing permanent rectal dysfunction with urgency of defecation; whereas surgery tends to have more permanent urinary impact. And both surgery and radiation cause problems with sexual function in about half the patients who start out with good function. Finally, radiation as the primary therapy makes subsequent salvage surgery very difficult if it made sense to resort to it. (The logic behind it is against ever doing that for salvage, particularly with today's higher doses achievable using IMRT. At WRAMC we go to a dose of 7800 cGy when feasible and the chance of local failure without concomitant distant failure should be in the single digits.) Again compared to EBRT, brachytherapy has more exclusionary criteria such as high grade tumors and patient prostate gland size. Earlier hopes for improved cure rates for seed implants have not materialized, and claims of better post-therapy potency remain unsubstantiated by unbiased data.

DEALING WITH MISCONCEPTIONS

Finally, let me present you with some misconceptions I have dealt with over the years in counseling and treating men with prostate cancer.

“I want the least invasive form of therapy possible so I want brachytherapy.” This man was influenced by comments in the popular media that said seed implants were less invasive than surgery. Well, that’s right, but they are more invasive than EBRT.

“I prefer seed implants because they have fewer side effects than external beam.” Wrong again. Seed implants are likely to cause more urinary problems. External beam is the gentlest way to go in terms of temporary side effects. The seed implant is about intermediate.

“I want the best chance of retaining sexual function, so I prefer seed implants.” Several studies made this claim for seed implants, but their conclusions are far from certain. Younger men tend to select seed implants; therefore they are likely to have better outcomes as far as sexual potency is concerned. This age factor applies to all the primary therapies. Surgery, EBRT, and seeds are likely equal in maintaining potency.

“I have a friend that swears by Therapy A, B, or C.” Patients should avoid this anecdotal evidence. Instead, why not attend an Us TOO support group meeting for a frank discussion with other men who have had various treatments and benefit from their experiences?

“I want the cancer out of there so I know that I am cured. The surgeon will be able to say he got it all out.” This is a frequent comment. For sure, the surgical patient will get the news (good or bad) faster with surgery. He will get the pathology results to tell him more prognostic information, and the PSA falls faster after the gland is removed than after radiation, which takes a few months to totally kill the cancer. However, if the cancer has escaped the capsule, “taking it out” won’t do any better than killing it with radiation, as most patients with positive margins will require radiation after any surgery to finish the job of eradicating tumor in the area of the prostate. “Taking it out” doesn’t imply a cure; the tumor may have metastasized (spread distantly) before surgery and these are the patients - those with micrometastases - who will likely not be cured whether they elect surgery or radiation as an initial option. Surgery or radiation—in

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either case you must take care of the local problem before it becomes a systemic problem. Whether getting it out or destroying it with radiation, the options are very similar in outcome. When the clinical evidence indicates a good chance of cure, I always recommend a careful review of potential side effects for that particular patient.

“Radiation has no back-up if it fails; failed surgery can be followed by radiation.” I hear this very often. The surgeon has to cut fairly tight around the prostate gland to excise it with some risk that cancer cells may remain. It’s true that residual cancer cells after surgery can be treated by follow-up radiation. On the other hand, when EBRT is the primary therapy, the radiation oncologist can and does add, as a matter of routine, a more generous safety margin than the surgeon can afford to do. So in that sense, EBRT doesn’t need a “back up” plan; it is its own safety net, so to speak. Furthermore, if a patient’s PSA rises after radiation, the site of failure would almost always be at a distant site and not the local site, and hormones would be the next step for what is at that point documented as what must be metastatic disease. Besides the fact that it’s not needed nor helpful, for reasons described above, there is also considerable reluctance to employ salvage surgery after failed radiation because of morbidities associated with that procedure.

QUESTIONS AND ANSWERS

Question: You have frequently mentioned “the tumor,” but more likely there are several tumors present. Is the treatment for that the same in that case?

Answer: Good question, and I should clarify that. The target, whether for surgery or for radiation, is really the entire prostate and part of the seminal vesicles. I have read that that the typical prostate cancer patient has 4.3 tumors. We would never just treat where the biopsy was positive. We always treat the entire prostate.

Question: I recently had the IMRT and it worked very well for me. I had a PSA of 4.9 and four months after therapy it had dropped to 2.3. My next follow-up PSA will be in two months. I’ve had zero side effects--nothing in terms of incontinence, ED, or bowel issues. I guess I’m very fortunate. My question is since I’ve experienced no side effects in the short term, what can I expect in the long term?

Answer: If you are going to get a permanent side effect, it usually starts around the sixth month after therapy is complete. If you haven’t experienced side effects by six months, you have reason to be optimistic for the long term. You still might have softer stools with certain foods or occasional diarrhea from things you eat and you’ll learn what foods to avoid over time.

Question: Let’s take a man who has recurrence after radical prostatectomy. Are there any new developments in radiation therapy about targeting local sites?

Answer: Salvage target definition is interesting. In the past, we thought a CT scan before surgery might give us better target definition in the event that salvage radiotherapy became necessary. But it didn’t work out because the anatomy is so changed. We know where the

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prostate bed was, and we have reliable techniques for standard radiation fields for that area. If a PSA rises after surgery we generally favor doing salvage radiation unless it is clear that the disease has metastasized. The best scenario is one that holds promise of a cure because the recurring cancer is within the prostate bed and nowhere else. And the only way to determine this is to give radiation and see if the PSA goes down as a result. The Prostatecint scan is sometimes helpful in that situation, such as when the margins were negative but we're contemplating giving radiation for a rising PSA, but it hasn't been the wonder test we had hoped for.

Question: How long does it take for the PSA to come down after IMRT?

Answer: I usually put it between 12 and 18 months after therapy until the PSA reaches its nadir, its lowest point, but it starts dropping almost immediately and usually goes down by half every 3-4 months until it starts to bottom out to the nadir. Some brachytherapy studies cite something like three or four years for the final nadir. But in my opinion, you get most of the drop in the PSA 12 to 18 months after treatment whether it is IMRT or brachytherapy. You just want it never to rise again, no matter what number it gets to.

Question: In our support group we have a man who has had both brachytherapy and external beam radiation. What is the take on that?

Answer: We've done it here at WRAMC a few times in certain situations. Let me be blunt and say that external beam is a way to make up for ineffective implants. Brachytherapy takes a lot of skill and you don't always get it perfect. When the two therapies are combined the radiation reaches further outside the prostate, which is needed for tumors that tend to reach outside the capsule. So, it can be used for a patient who really wants the seed implant, but he's Gleason 7 or 8 and there is concern that the disease has escaped the prostate. That's probably the best reason you would combine them if you are willing to deal with the increased side effects without any known improvement in the chance of cure. Some men have heard so many good things about seed implants from the media or from friends, or occasionally from their doctor, that they want the seed therapy even though they're a high risk patient, and that's one way of effecting a compromise.