## “Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]

Brad Power
May 15, 2024

*“Many patients are not aware that the radiation that we give today is not the same radiation that they might have heard about 20 or 30 years ago, which caused a lot of side effects.”* – Chandra Kota, PhD

*“We used to treat the whole prostate with a uniform dose. But now with multiparametric MRI, we can see the areas of disease more clearly. We incorporate that into radiation planning. We keep those areas at a higher dose than the rest of the prostate with hopes of controlling the tumor better.”* – Chandra Kota, PhD

*“We could use more patient advocates. Those who have had good experiences should speak up on our behalf, maybe with their friends and families, so that people are not scared of radiation and realize that it has a good role to play.”* – Chandra Kota, PhD

**Meeting Summary**

Surgery or various kinds of radiation can often serve as the first line of treatment to kill solid tumors and provide reasonably durable local control for cancer patients. Radiation therapy can be delivered from outside the body (external beam), with implanted radioactive sources near the tumor (brachytherapy), and more recently with radioactive molecules that bind to targets on the tumor cells (radioligand).

Most doctors believe that surgery and radiation are equally effective. Surgery may offer a slightly higher long-term cure rate than radiation. Radiation usually doesn't require a stay in the hospital, and you may be able to carry on with your daily life. The disadvantages of surgery include the inability to kill microscopic disease around the edges of the tumor, and difficulty in tolerating the surgery and anesthesia. Disadvantages of radiation therapies include a cumulative tolerance limit of various tissues which can limit re-irradiation. Radiation can be delivered at different dosages depending on modality and clinical goals.

Understanding and navigating the radiation process can be challenging since it is complex and often involves your active participation. Technical and clinical advances in the past few decades have created new opportunities for radiation therapies that offer better outcomes.

Chandra Kota, PhD, Senior Medical Physicist at ChristianaCare, has first hand experience with many radiation therapy techniques and is uniquely qualified to describe the various radiation processes to help you better understand and navigate this complex treatment modality.

***What should you know about getting radiation therapy?***

- There are different radiation therapies (photons, electrons, and protons). Different types of radiation deposit energy differently, leading to varying biological effects. You need to have a personalized approach to your radiation therapy.

## “Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]

- The benefits of proton therapy (over other radiation options) include better dose distributions and reduced damage to healthy tissues.

***What is new in radiation therapy?***

- Real-time guidance technology for radiation (combining a scanner with the radiation delivery) can decrease margins and spare surrounding tissues.
- “Biologically-guided radiation therapy” uses an injected radiotracer which lights up solid tumors to guide the radiotherapy beam during delivery of radiation, increasing accuracy even if you move.
- New radiation technologies (such as volumetric radiation) are much faster than the older technology. You may lay there for five minutes instead of the twenty minutes that you had to earlier.
- Radiosensitizers, techniques to sensitize cancer cells to radiation, are in research, but none are demonstrating major effects yet.
- With radioligands (e.g., leutetium), a gap in delivery, instead of a straight course, yields better patient survival.

***What can you do to see if radiation therapy is right for you?***

- Review our discussion with Carl Rossi of California Protons for more details on proton beam therapy and how it compares to other radiation options and surgery.
- Read about ongoing research in radiation.
- Explore ways to optimize your radiation treatment to better spare nearby critical structures, like your urethra for prostate cancer patients.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

**Meeting Notes**

## KEYWORDS

radiation, patient, treatment, protons, beams, dose, prostate, radiation oncologist, field, tumor, target, proton beam, called, radiation treatment, therapy, machine, treat, photons, deliver, people

## SPEAKERS

Chandra Kota (70%), Allen Morris (11%), Brad Power (9%), Rob Weker (7%), Richard Anders (3%)

## SUMMARY

Chandra Kota discussed the latest developments in radiation oncology, highlighting the importance of interdisciplinary collaboration, technological advancements, and personalized treatments. He discussed the evolution of radiation therapy technology, with a focus on improving treatment times and reducing off-target toxicity. He also discussed the latest developments in radiation therapy for prostate cancer, including improved dose distribution and emerging technologies. The conversation also touched on the potential of radiosensitizers in cancer treatment and the need for more patient advocates to bridge the gap between radiation oncology and laboratory medicine.

## OUTLINE

### Radiation therapy for cancer treatment.

- Chandra Kota discusses radiation treatment for cancer, providing insights as a medical physicist.
- He explains the complexity of oncology, mentioning various specialists and outside organizations working to improve patient care.
- He highlights the challenge of keeping staff and physicians educated in the face of rapidly changing knowledge and clinical pathways.

### Radiation oncology, jargon, and treatments.

- In the radiation treatment process, the patient consults with a doctor, undergoes simulation to develop a treatment plan, and receives targeted radiation treatment for localized cancer.
- Medical doctors, physicists, therapists, and nurses collaborate to provide radiation oncology treatment.
- Technical staff (biomed engineers, biomedical technicians) maintain and repair radiation machines during treatment.
- Dr. Kota explains the history and advancements in radiation therapy, including multileaf collimator (a beam targeting device) and volumetric arc therapy.
- He demonstrates how these advancements improve targeted radiation dose delivery.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

## Radiation types and their effects on cancer treatment.

- Dr. Kota explains differences in radiation therapy types (photons, electrons, protons) and their applications.
- He highlights the benefits of proton therapy, including better dose distributions and reduced damage to healthy tissues.
- Different types of radiation deposit energy differently, leading to varying biological effects, and patient selection is crucial for optimal treatment.
- He discusses different dose ranges for radiation therapy, including partial killing of tumor cells and ablative lesions.

## Radiation therapy for prostate cancer, including dosage, delivery methods, and side effects.

- Radiation therapy can treat non-cancerous conditions like trigeminal neuralgia and osteoarthritis, and modulate inflammation at lower doses.
- Dr. Kota discusses challenges in radiation therapy for prostate cancer, including margin reduction and bladder filling.
- He discusses guidance technology for prostate cancer treatment, highlighting its ability to decrease margins and spare surrounding tissues.
- He also mentions biologically-guided radiation therapy using PET imaging agents, which can localize solid tumors for treatment.

## Advancements in prostate cancer radiation therapy.

- Dr. Kota discusses radiopharmaceutical therapy for prostate cancer, including different types of emitters and their effects on cells.
- Investigators explore novel techniques for personalized radiation therapy, including targeted biopsies and multi-parametric MRI.
- He discusses challenges in the radiation therapy field, including lack of policy support, reimbursement issues, and limited funding for research and education.

## Radioligands and their potential for cancer treatment, with mentions of investment and innovation.

- Pharmaceutical companies are investing heavily in radioligand therapy.

## Proton beam therapy for cancer treatment, reimbursement challenges, and new technologies.

- Rob Weker shares his experience with proton beam radiation therapy for pancreatic cancer, highlighting the challenge of reimbursement.
- Dr. Kota discusses the challenges of treating cancer with radiation, including the need for more targeted treatments and the potential for unintended side effects.
- Rob Weker expresses suspicion that his initial radiation treatment for testicular cancer may have contributed to the development of pancreatic cancer 20 years later.
- He mentions proton therapy centers in Philadelphia and UPenn.
- Dr. Kota discusses older proton technology and its limitations.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

## Radiation therapy techniques and their differences.

- Allen Morris questions Dr. Kota about medical physics, specifically the differences between historic conformal radiation therapy and newer techniques like IMRT and volumetric arc therapy.
- Dr. Kota describes advancements in radiation therapy technology, including multileaf collimators and volumetric arc therapy.

## Optimizing radiation therapy with proton beams.

- Allen Morris explains that using more beams in radiation therapy is a medical radiation physics concept, and only tangentially the purview of radiation oncologists. That the number of beam angles are a physical (physics) way to reduce off-target effects.
- Dr. Kota mentions that optimizing the timing of proton beam delivery can help reduce the entrance bath and improve treatment outcomes, but this may require faster machine capabilities and more complex math.
- Richard Anders wonders about theoretical minimum radiation delivery to normal tissues, resulting in limiting off-target toxicity, given an infinite number of beams.
- Dr. Kota explains that with photons, there is no theoretical minimum, but with protons, it depends on collimation and beam overlap.

## Radiosensitizers for cancer treatment, with a focus on boron neutron capture therapy and hyperbaric oxygen.

- Dr. Kota mentions boron neutron capture therapy as a potential radiosensitizer, but notes that it has limitations.
- He explains the role of medical physicists in radiation oncology, including planning and overseeing treatments.
- Medical physicists work with radiation oncologists to ensure quality and accuracy in radiation therapy.

## Radiation oncology, medical physics, and patient advocacy.

- Allen Morris discusses that radiation oncology and pathology/laboratory medicine are complex fields involving many types of professionals within each. And that if you have an understanding of the differences in the educational backgrounds of those expert types, you can better direct the “conversation”.
- He points out that ADT treatment combined with Radiation therapy is established as a synergistic combination and the combination continues to mature by answering corollary questions such as what duration is optimal for various patient contexts.
- Dr. Kota encourages more patient advocacy to address radiation fears and promote its role in cancer care.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

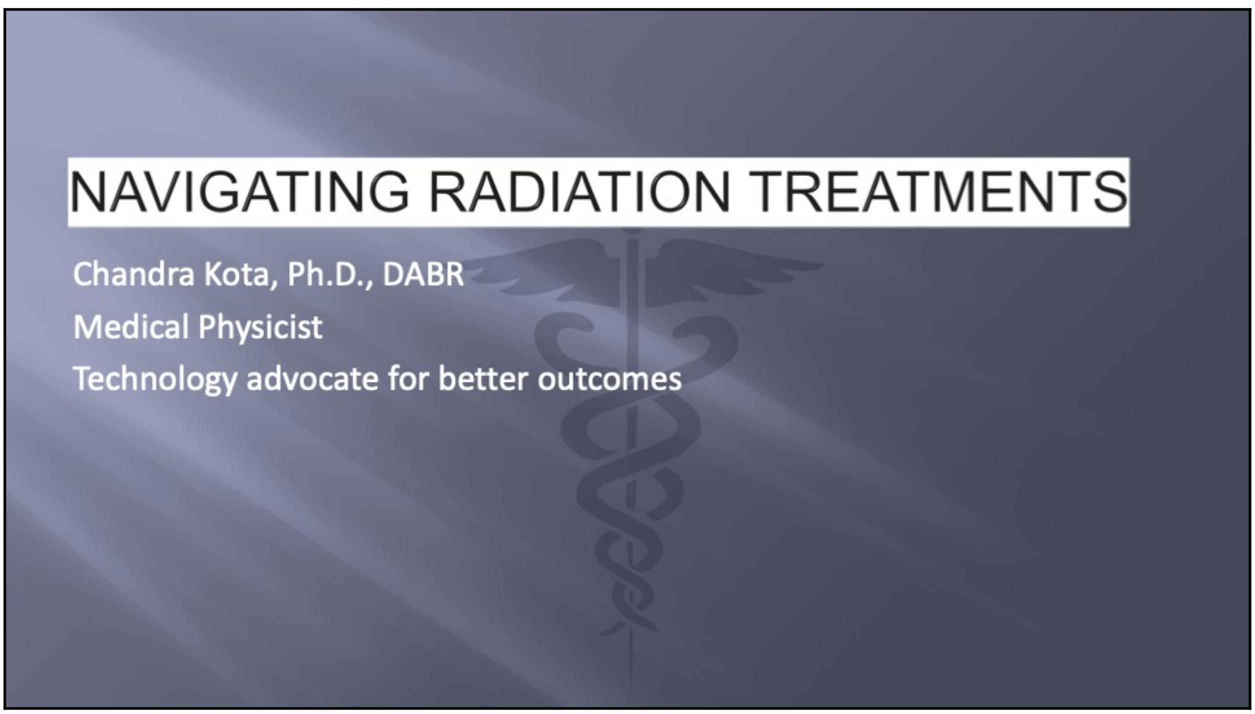
TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

Today we're honored to have Chandra Kota with us. He's going to give us some background and information about how to think about radiation treatment for cancer. Chandra is a longtime friend. He's been involved with our activities for many years. He's currently based in Delaware. When I got to know him, he was doing something at Yale. He's a medical physicist. He works with radiation oncologists. Early on, I had to learn that there's a difference between the radiation that's used for diagnosis, and the radiation that's used for treatment, and Chandra had to keep correcting me on those distinctions.

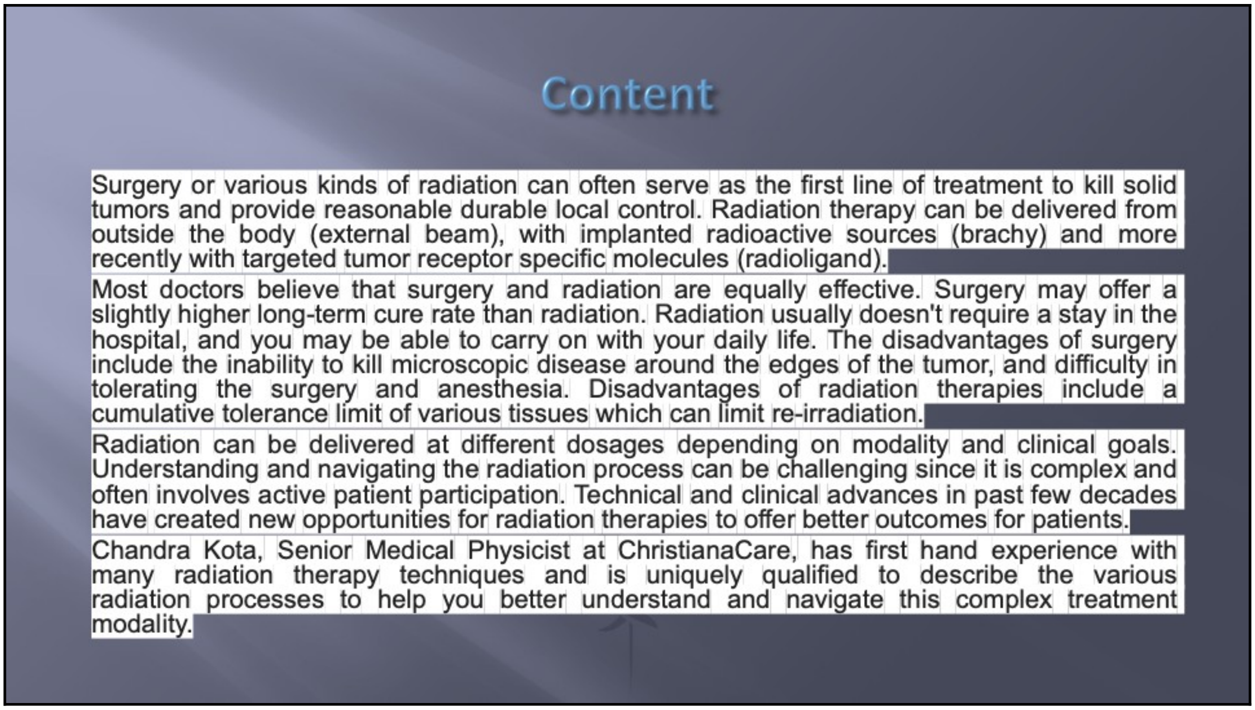
This is for information purposes only, and is not medical advice. Please consult your doctor. We're trying to give you information that will help you in conversations with your medical team.

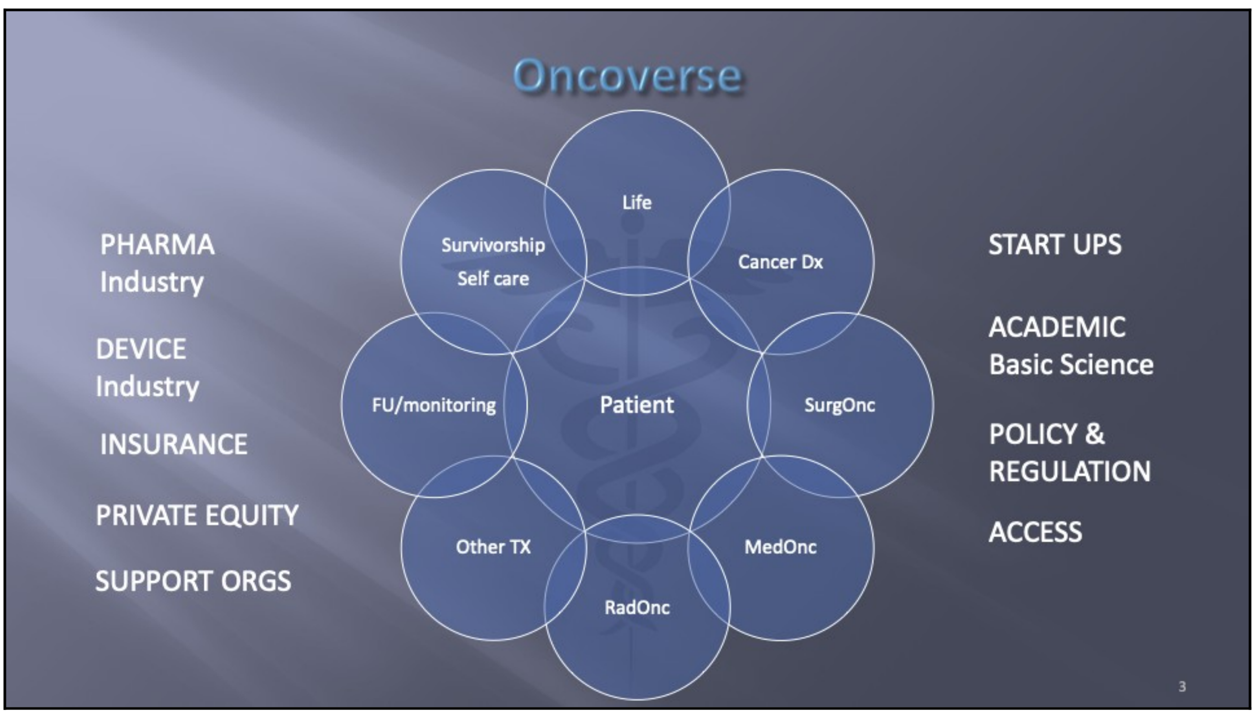
We're a patient-led organization. We are volunteers. We depend on the kindness of members to make donations. Please donate if you're so inspired.




Chandra Kota 1:48
I want to share some thoughts about radiation and its place in treatment for cancer. I am what's called a “medical physicist”. It's a very niche field. We are more of experts on the technology side to deal with radiation, both in radiation therapy as well as in diagnostic imaging. We help the radiation oncologist and the medical doctors in designing the treatment plans and overseeing the delivery of treatments, and quality control and quality assurance. You could think

of it like a pharmacist, but also doing other things beyond just what pharmacists might do on the medical oncology side.

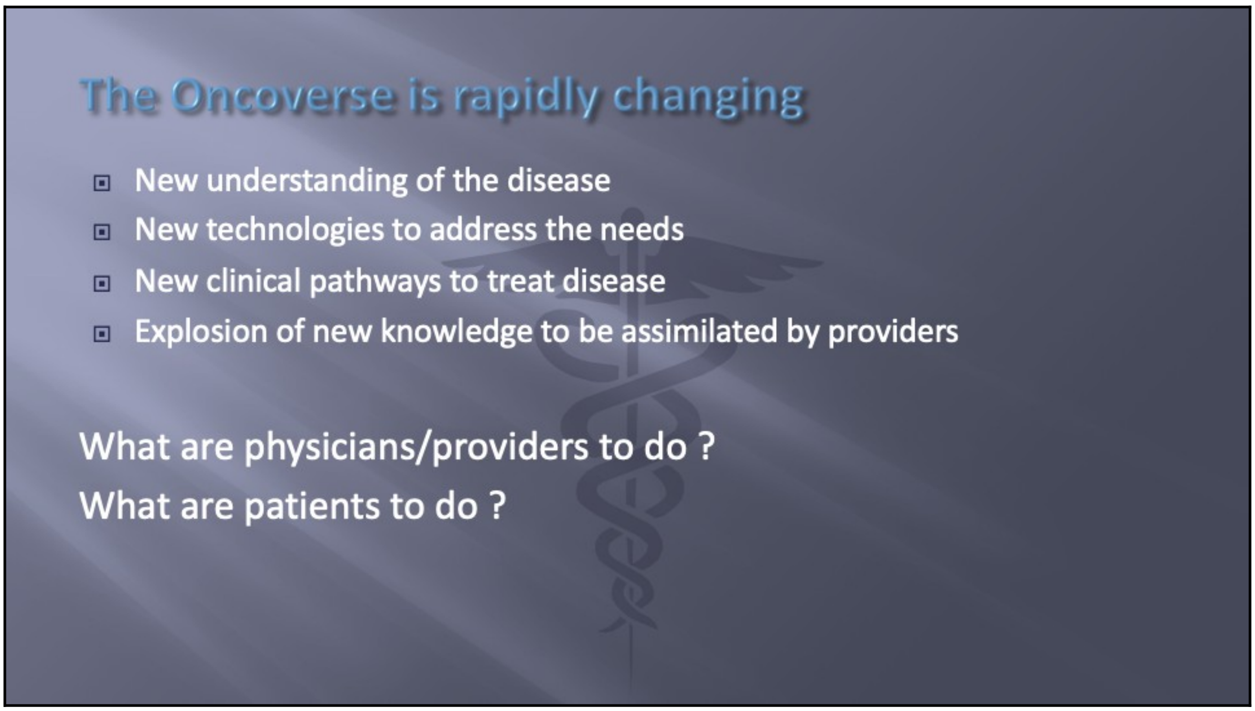



Chandra Kota 2:58
Thinking outside the box of my day job, I like to think of this whole universe of oncology as the “oncoverse”. It's very complicated.

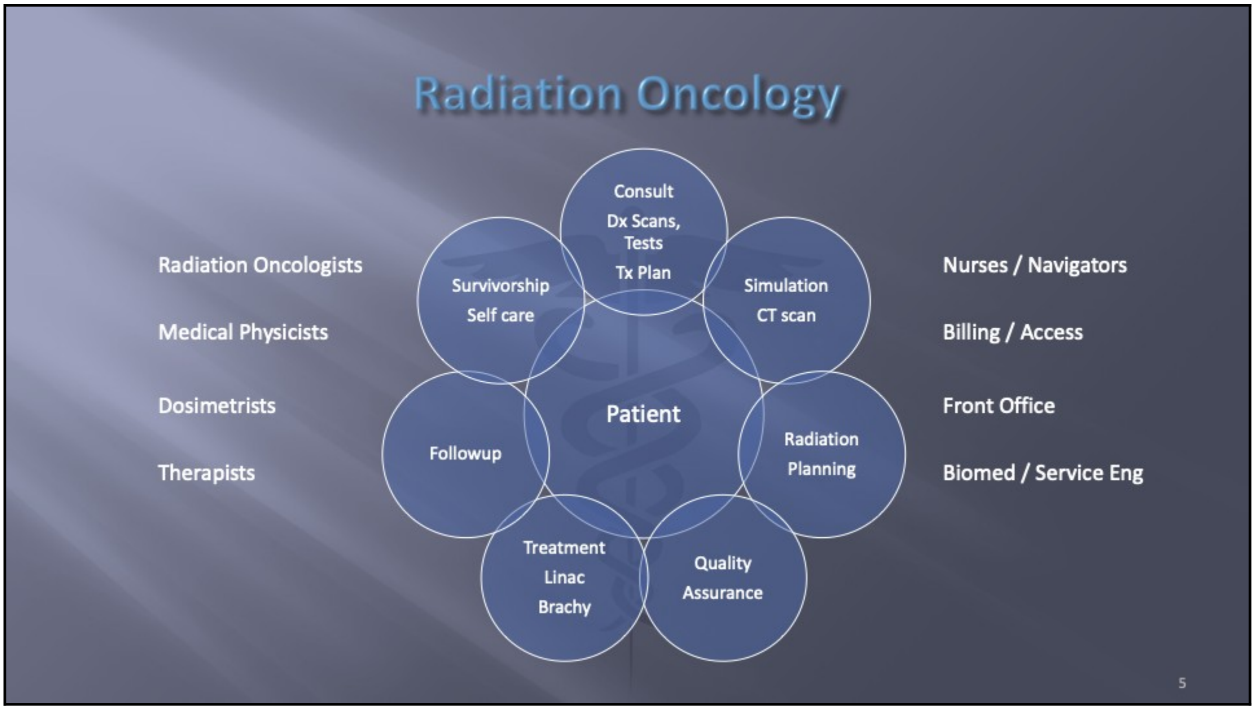
**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

As we get older, most of us are likely to get some kind of cancer. That's just the body's natural aging mechanism. Then you go through the diagnosis and then you meet a bunch of specialists who are going to try to make things better for us, like a surgical oncologist, medical oncologist, radiation oncologist. Then there are all these other people on the outside that are also working diligently trying to make things better for everybody. Like there is pharma. There's devices. There's insurance people. There's private equity, trying to invest money and support innovation. And the support organizations, a lot of them are just volunteers, like the one that Brad runs, which is more focused towards trying to find treatments outside the standard of care. There are other support organizations that are there. So if patients need somebody to talk to or, or go visit and get some help, they're there. For example, I volunteer at one, Cancer Support Community for Greater Philadelphia. It's a great place. And there are others.




The problem is, since about 30 years ago, everything's changing so fast. There's new understanding of disease, and there's new technologies and new clinical pathways, and there's just an explosion of knowledge. I'm from the provider side, so we take care of patients right in the hospital setting. I just see so much new knowledge coming out. It's a challenge to keep the staff educated, the physicians educated. How do you disseminate all this knowledge, and all these pathways so they can get down to the clinical level so that patients can benefit from it?

## “Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]




Within radiation oncology, we can think of the field like this. As a patient, you would come in and consult with a doctor. The doctor might order more scans and come up with a clinical treatment plan. There's a bunch of jargon that's used.

You will move on to the next step, which is called a “simulation”. That's usually done with a CAT scan. We plan the radiation, how the radiation beams will be directed at the tumor, based on the CAT scan. Radiation treatment is a very targeted treatment. We treat well defined, localized disease. We cannot treat diffuse disease. Once it's well defined and localized, we target it using radiation planning, and then we do a lot of quality assurance to make sure that whatever has been planned is the radiation that's going to be delivered through the treatment to the patient.

Then there's the treatment itself. It could be an external beam using linear accelerators. We usually call them “Linac” for short. There's a different procedure called “Brachytherapy” where you insert radioactive material into the target area. As far as the prostate goes, seed implants are very common. There's also high dose rate brachytherapy for the prostate. We do a lot of prostate seed implants.

After that there is a follow-up with scans to look for response assessment.

Then pretty much all patients are left on their own. If something bad happens, they come back into the healthcare system, and then the cycle starts all over again.

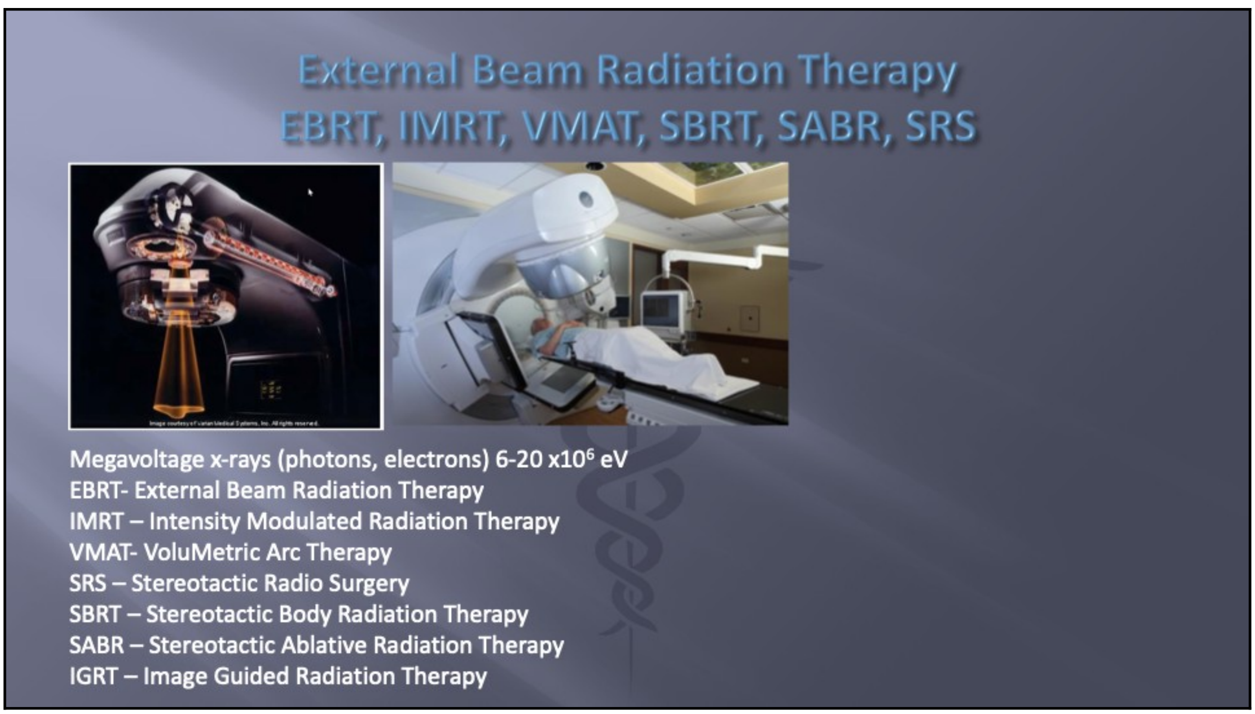
Within our field we have radiation oncology, the medical doctors who are trained to understand radiation, and also other parts of oncology. They have a fairly decent knowledge of medical oncology and surgical oncology because they work with those two specialties in a multidisciplinary way, trying to figure out how to combine treatments to maximize benefit for our patients.

After that, we have medical physicists who, like I said, are the technical side. We understand radiation. We understand the radiation machines. We understand treatment planning. We oversee dosimetrists (an analytical member of the radiation oncology team who designs, generates, and measures radiation dose distributions and dose calculations) and therapists, who are the staff you might encounter if you ever had these treatments. They're the ones who put you on the table, take care of you, position you on the table, make sure you're in the right position, and then they administer the treatment with the machine.

Of course, there are nurses and navigators who facilitate the process for the doctors and make everything work seamlessly.

Unfortunately, the field is such that billing and accounting people are also very important. Everything's become prior authorization these days. It's very important for the staff to keep on top of the billing companies to make sure they get all the approvals in time, so that we can deliver the treatments in a timely manner without any significant delays, which could impact care.

These are very complex machines. So you have biomed staff and engineers who will fix the machines if they break. If any of you had treatments, you might have experienced in the middle of a treatment a machine might break, and then we are going to fix it and resume the treatment.




There's a lot of jargon in our field. External beam radiation therapy is EBRT.

The next one is IMRT, which is intensity modulated radiation therapy.

There's VMAT, which is VoluMetric Arc Therapy.

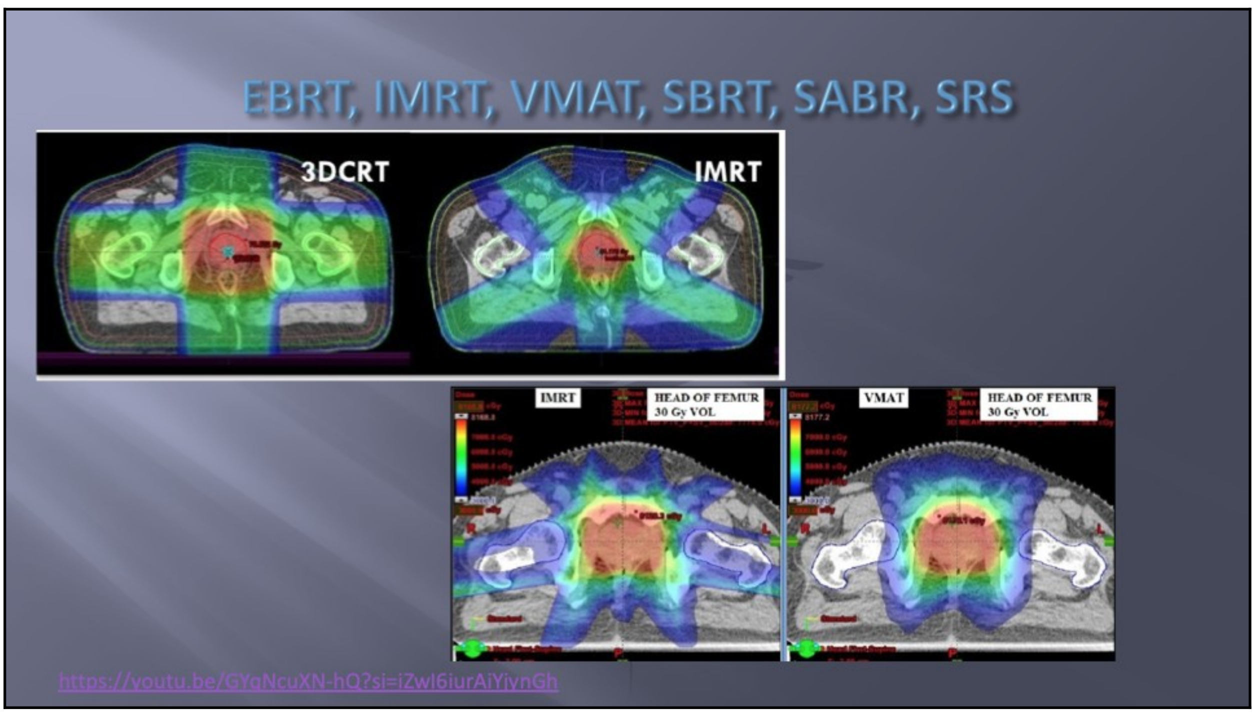
There's SBRT, stereotactic body radiation therapy.

SABR, which is stereotactic ablative radiation therapy

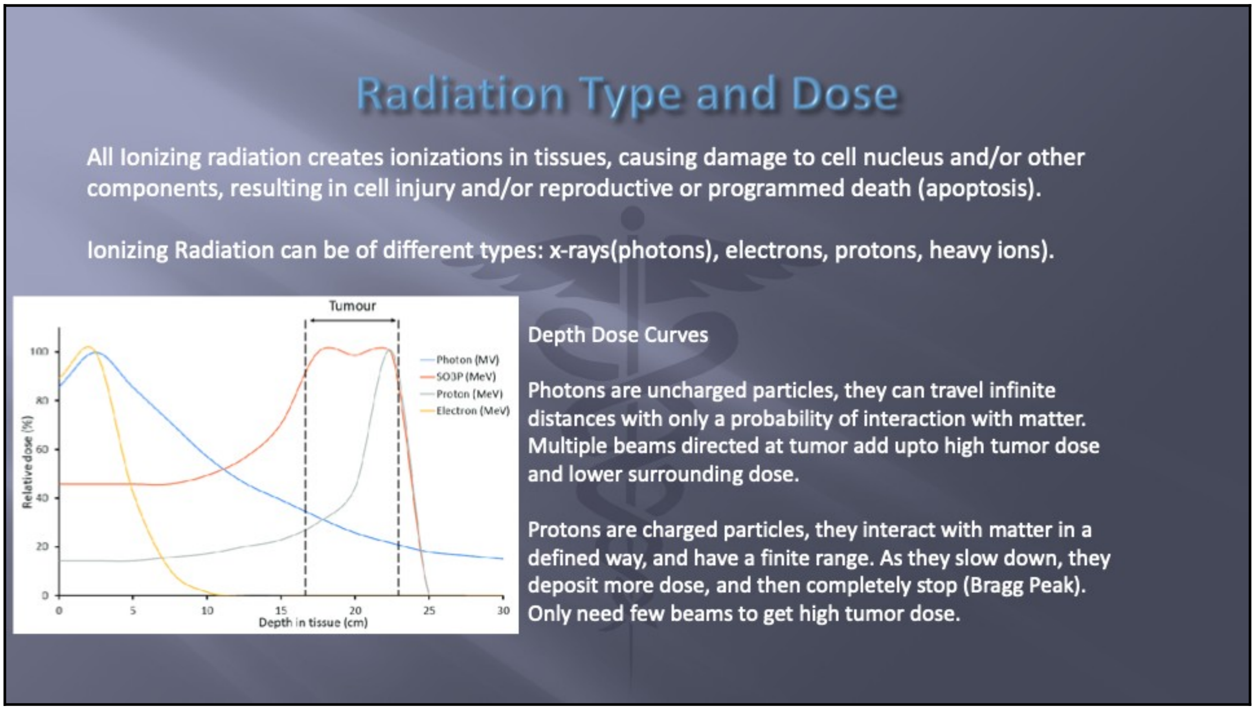
SRS or just stereotactic radiosurgery.

A lot of this jargon is historical in nature and also related to how we can bill for things because it's a very procedural-based field. We do different tasks, and we are allowed to bill for each of those individual tasks. The acronyms got tied in with what the billing folks decided when new things came out. This is not necessarily very helpful or very reflective of what's really happening.

To give you a brief overview, most of the treatments we do with external beam radiation are machines called “Linacs” (linear accelerators). Protons are different. These are really high energy photons. They're so high that you cannot just generate them like you would with an X-ray tube. There are special devices called “linear accelerator tubes”. That's why the name is “Linac”. The patient will lay on the table, and this machine rotates around and delivers treatment according to the radiation plan.




Historically, like when I first entered the field about 30 years ago, it was a very simple and a cool treatment. We could only target the fields very crudely around the prostate. For example, I'm giving examples of prostate here. That's a prostate. It used to be called a three dimensional conformal treatment. We used to use four directions to attack the prostate. But a lot of other organs in the path of these beams got the radiation dose as well, and we had no good way to control it. The next significant development technically was something called a “multileaf collimator”. That led us to shape the beams a lot better. We could tailor the radiation dose to the target and spare the rectum and the bladder much better than we could with three dimensional conformal therapy. The one after that the came is called the VoluMetric arc therapy, which is similar to the IMRT except that the machine is continuously rotating around the patient. So the radiation dose is tailored even better than those others.

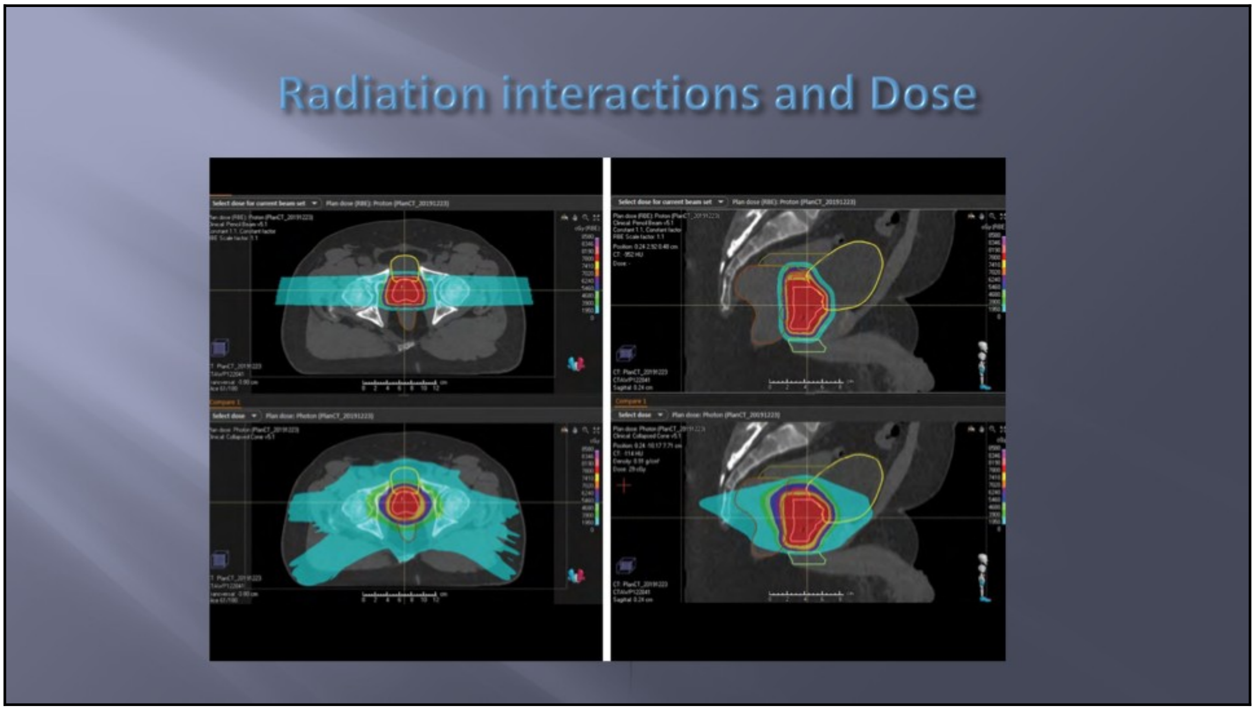



There are different kinds of radiation most commonly used. X-rays and electrons are very common.

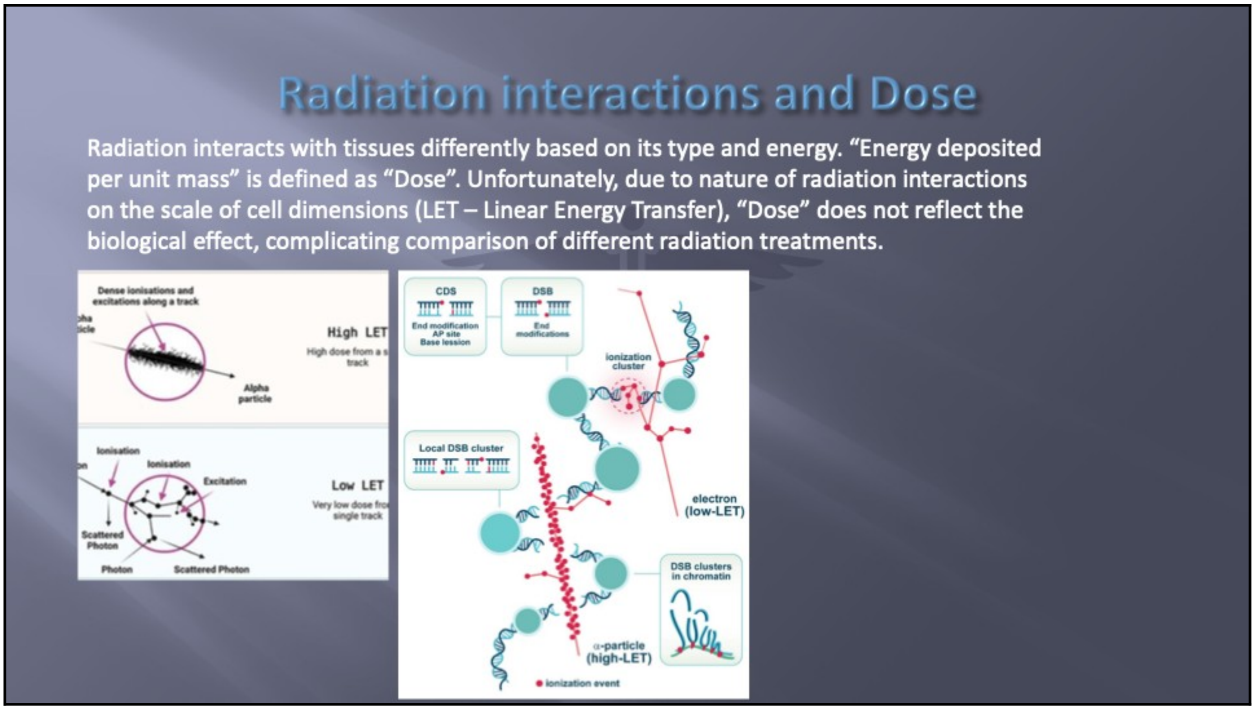
Photons are less common, but more so these days. There are several facilities, but not as many as for conventional radiation. I want to spend a little time explaining to you the main difference. Photons are called “uncharged particles”, that means they can travel infinite distances in matter, until they interact with something. They tend to have within a patient what is called “the depth dose distribution”. They tend to have what the blue curve indicates: most of the doses deposited towards the surface of the patient, and less where the tumor will be located. There's a lot less dose there. So the way we achieve a treatment is to direct the radiation beams at the tumor from different directions, so that the tumor dose becomes more than the surface dose, based on the number of beams we use.

Electrons have a dose distribution. They don't go very far because they're charged particles, and they interact with matter in a very definite way. But they're not very useful because they cannot be focused very well. They're very light particles, so they scatter a lot within the body. They're not used in a very precise way for precise treatments.

Protons, on the other hand, are much heavier than electrons. They have a very characteristic depth dose curve. This is called “a Bragg Peak” (a sharp peak in the delivered dose followed by a rapid falloff). The entrance dose is very low because these are high energy protons. As they get slower, they interact more with matter, and they deposit a lot more dose. Then they eventually come to a complete stop. The benefit of protons is that beyond this point, there is no dose at all. So you're able to spare things, in theory, much better than you can ever hope to do with photons.




This is an example of a prostate plan with conditional photons and protons. You see here that with photons, there's a lot more dose all around because we have to come around from different directions. But with protons, you don't need to do that. You only need a few beams, often it's two or three. It's much better defined, sparing lots of other tissue.



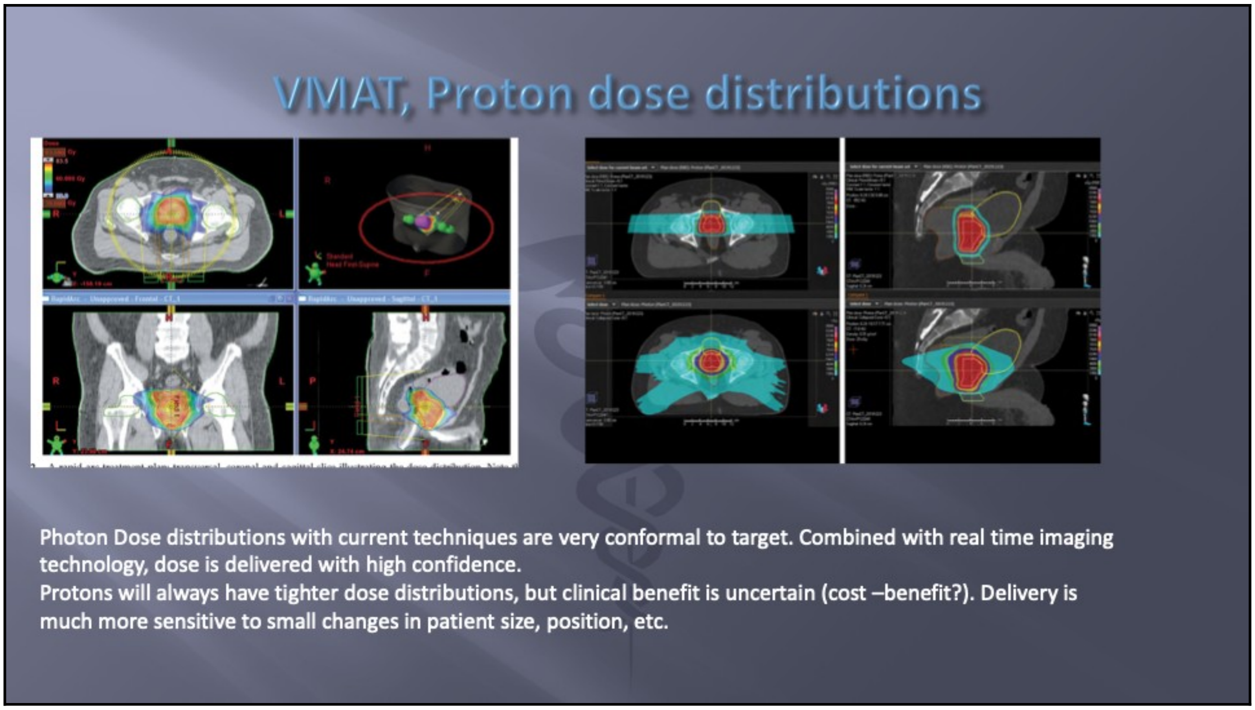

There is no doubt or any discussion about the fact that protons create much better dose distributions. The only challenge is, “Does it really benefit the patient?” And, “Is it worth the cost for all treatments?” There are some cases where protons are definitely better. But the question we have within the field, “Is it essential to treat every single patient with protons?” There needs to be a lot more patient selection going on.

The other different radiations interact differently and deposit the dose differently. You might have heard about radiation dose, which in physics is defined as energy deposited per unit of mass. Unfortunately, the ways it is deposited are so different among different kinds of radiation, that the dose by itself doesn't reflect biological effect.

There are two differences I want to point out. It's interesting because you might hear about this from the radiopharmaceutical treatments point of view as well. Low dose, low-LET, is low linear energy transfer. Those ionizations are very sparse at a cellular level. They might cause single strand DNA damage. Occasionally, they might cause some double strand DNA damage. It's conventional wisdom that you need several double strand damages to effectively kill a cell for reproductive death, that this higher emitted radiation, which is alpha particles, or heavy ion beams, for the very, very distal end (sites located away from the center) of a proton track. When the protons almost stop like that, it becomes really high energy radiation. These are very dense ionization tracks. They could create such a dense ionization that if they were to pass through the nucleus, they would create several double strand breaks, so there is no chance for the cell to survive. That's a difference because the same dose may reflect a different biological effect. Within our field, we try to address that by assigning different radiations and different relative biological effect values. So it's not a very sophisticated way of thinking about dose.

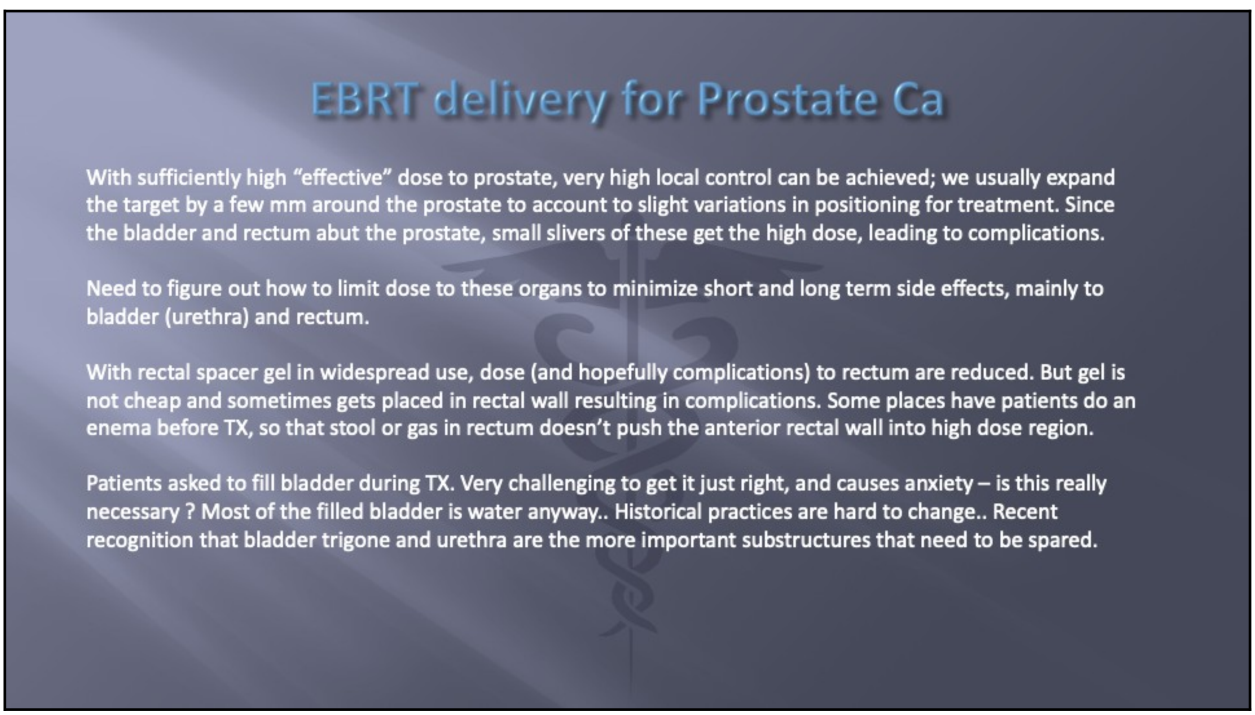
To complicate things further, the effect of radiation on tissue depends on the radiation type, the dose rate, and the total dose. The dose rate is very interesting. Conventionally, we used to treat about one and a half to about four Gray per fraction. That's what we call “a daily treatment”. We call that a “fraction”. If you're getting one of these more intense treatments, it's about seven to 20 Gray per fraction. It turns out that if you give a conventional radiation treatment of the prostate, depending on the diagnosis and the staging, it's about 70 to 80 Gray in 2 Gray fractions, whereas for SBRT or SABR, it's forty Gray in eight Gray fractions, but the tumor control is equivalent. A smaller dose in Gray just because it's more per fraction. So it turns out that in this dose range one and a half to four Gray, there is only partial killing of the tumor cells, cells can repair themselves, as can normal tissue cells. So that's why you need higher doses. But once you start going above eight Gray, the density of ionization within tumor cells increases such that there is not as much repair going on, so you're killing more of the cells effectively. That also means that if normal cells’ tissues were to be in this dose range, they would also die, so you have to be very, very careful and deliver this treatment very precisely, so that all the surrounding normal organs are much better spared than in a conventional treatment. There is yet another dose range which is not used for prostate cancer or for cancers of all. If you give a very very high dose per fraction and upwards of 50 Gray, radiation results in ablative lesions, that is, you kill everything that you touch. It is used in treating non-cancerous benign conditions, such as stretching trigeminal neuralgia, which is facial pain, essential tremors, etc. On the other hand, we are also more recently realizing, or noticing, that at lower doses, radiation seems to modulate inflammation. Low dose RT (radiotherapy) is providing good pain control for osteoarthritis. This treatment technique had fallen out of favor in this country, but in Europe they do things very differently. There is a lot of low dose RT literature in Europe. We're just about seeing this resurgence of interest in this technique in the United States as well, to benefit patients.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**




In terms of dose distributions, which I described earlier, with the VMAT technique the machine goes around the patient and conforms the dose as well as it can. That's the latest state of the art that we have with photons.

And of course, protons use different techniques, and they definitely create better dose distributions than photons. The question is, “Is it clinically beneficial for the added cost?”



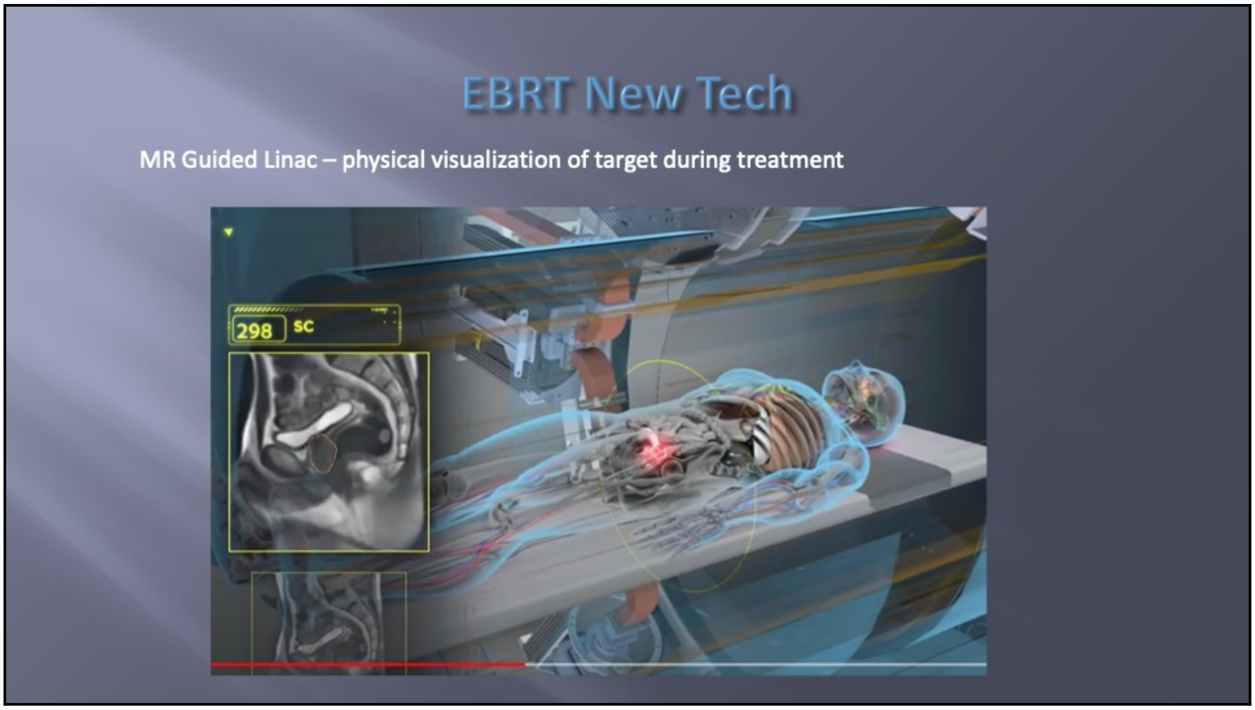
### “Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]

A few thoughts about external beam delivery for prostate cancer. We know that if we give a very, very high dose to the prostate or any other tumor, we can achieve very good local control. So that's not the problem. In the olden days, we weren't quite sure what we were hitting with the radiation beams, so we used to add a margin around the target. Because of that margin, the rectum and the bladder used to be subjected to higher doses as well, and those created complications. But these days, we have imaging incorporated into the linear accelerators. So we are able to see the target as we treat it, so we can decrease those margins and make it tight. We are able to spare those organs much better, thereby decreasing the side effects.

A recent development is one of rectal spacer gel in which a hydrogel is placed between the rectum anterior rectal wall and the prostate. That helps us in separating the rectum away from the prostate so that it receives very, very little high dose. But if the gel is not placed accurately by the physician doing it, it can get into the rectal wall, and that can cause unnecessary complications for patients. There have been some reports in the literature. It has to be done carefully.

Something that is a pet peeve of mine is we ask patients to fill their bladder during treatment. This is very challenging to just get it just right. And oftentimes, we have to get them off the table and have them sit around and drink more water, and then try to hold it all in. So this is stressful. We're not quite sure whether it's necessary because most of the bladder is water anyway. But this is historical practice. In the field, we try to educate ourselves and try to do clinical research at the multi-institutional level to see if we can change these things. There is increasing recognition that it's not the whole bladder that's as important to control the side effects as it's a bladder trigone in the urethra (a triangular shaped region at the base of the bladder ). So we try to see if we can create treatment plans that can decrease those to the substructures so that these kinds of treatments can be easier for our patients.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**

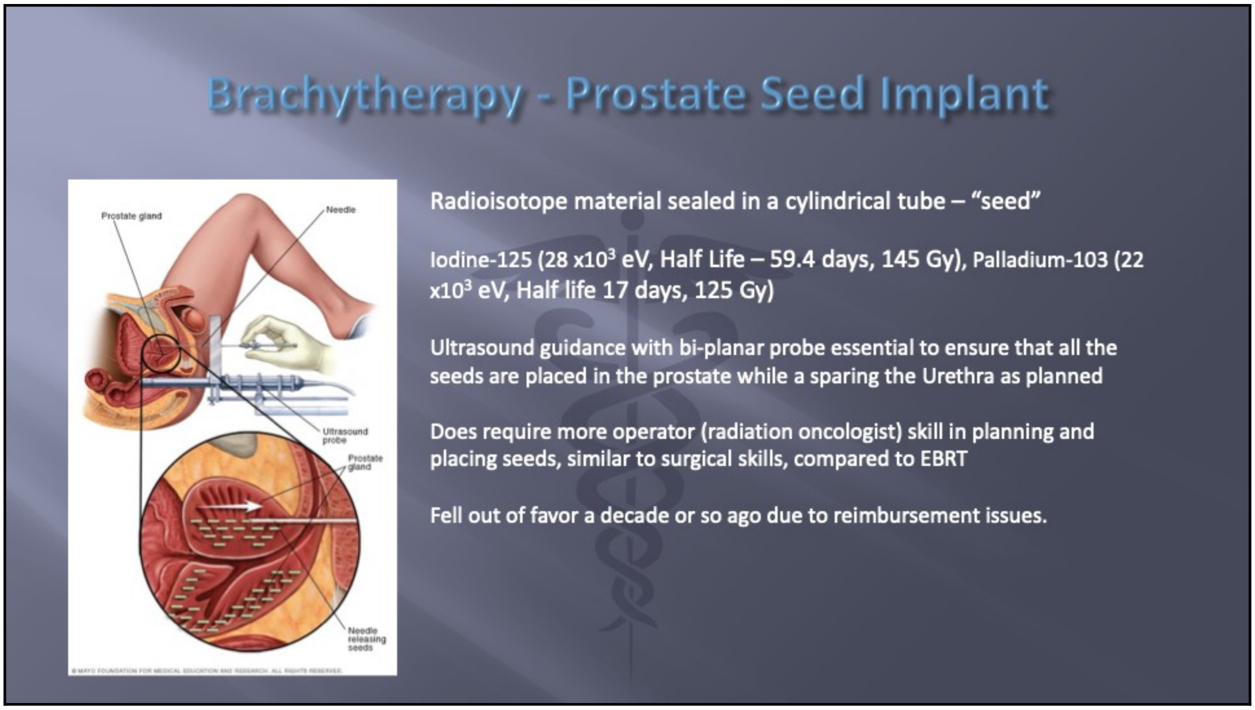



There were two different emerging technologies in external beam. One is the MR (magnetic resonance) Guided Linear Accelerator. MR guidance is very interesting because it provides much, much better soft tissue contrast, as you can see in this little cutout here. This is a schematic showing the MRI images acquired with the patient on the table. You're able to see the prostate very clearly in this sagittal view (a vertical plane which passes through the body longitudinally). The benefit of this is you'll be able to decrease your margins so that you can spare the urethra and the rectum much better than you can conventionally. There's been some very interesting work done at UCLA with this technology, where they showed they could decrease the margins on the prostate, treat very tightly to the prostate, thereby decreasing genitourinary side effects.

**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**


The other one that's come about more recently is a PET-guided linear accelerator, where if you were to inject the patient with a PET isotope, the tumor areas would light up, and you're able to target those areas, and then treat them with this linear accelerator. That's called “biologically-guided radiation therapy”. It would not be as useful as a pharmaceutical therapy because that's too diffuse, but if you had a limited number of solid tumors that can be localized using PET imaging agents, this could be an interesting machine on which we can treat patients very successfully.

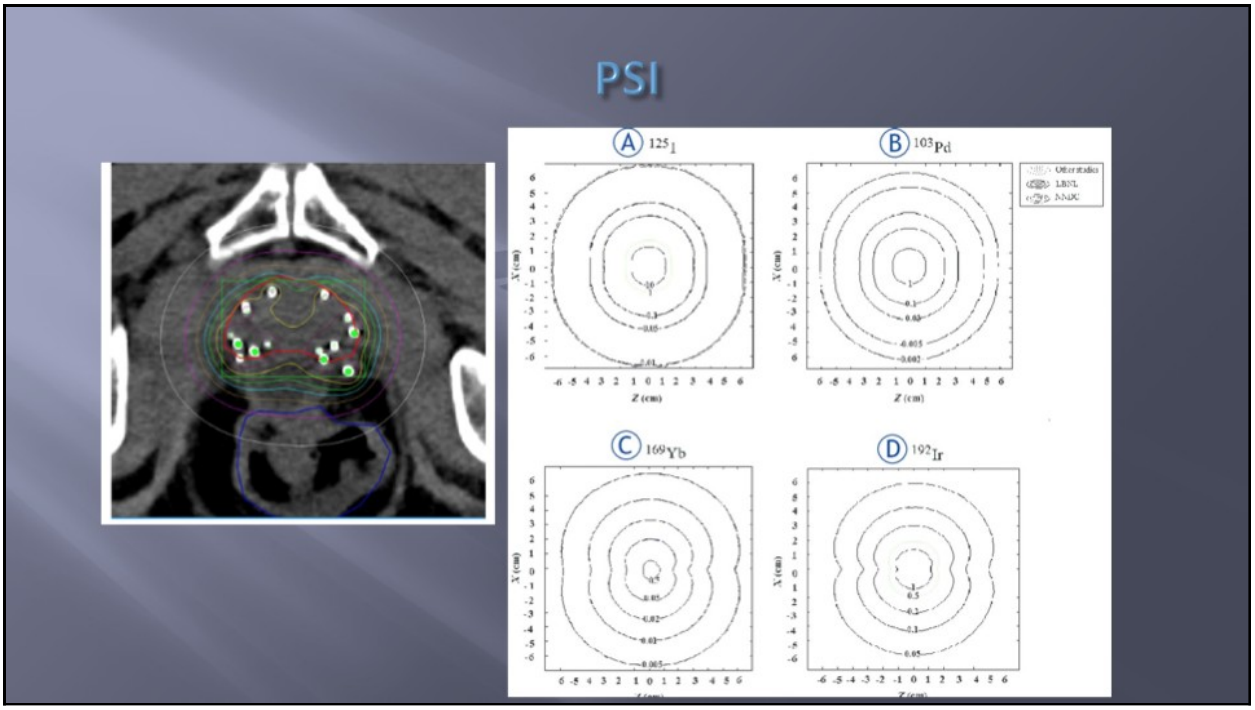
**“Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]**



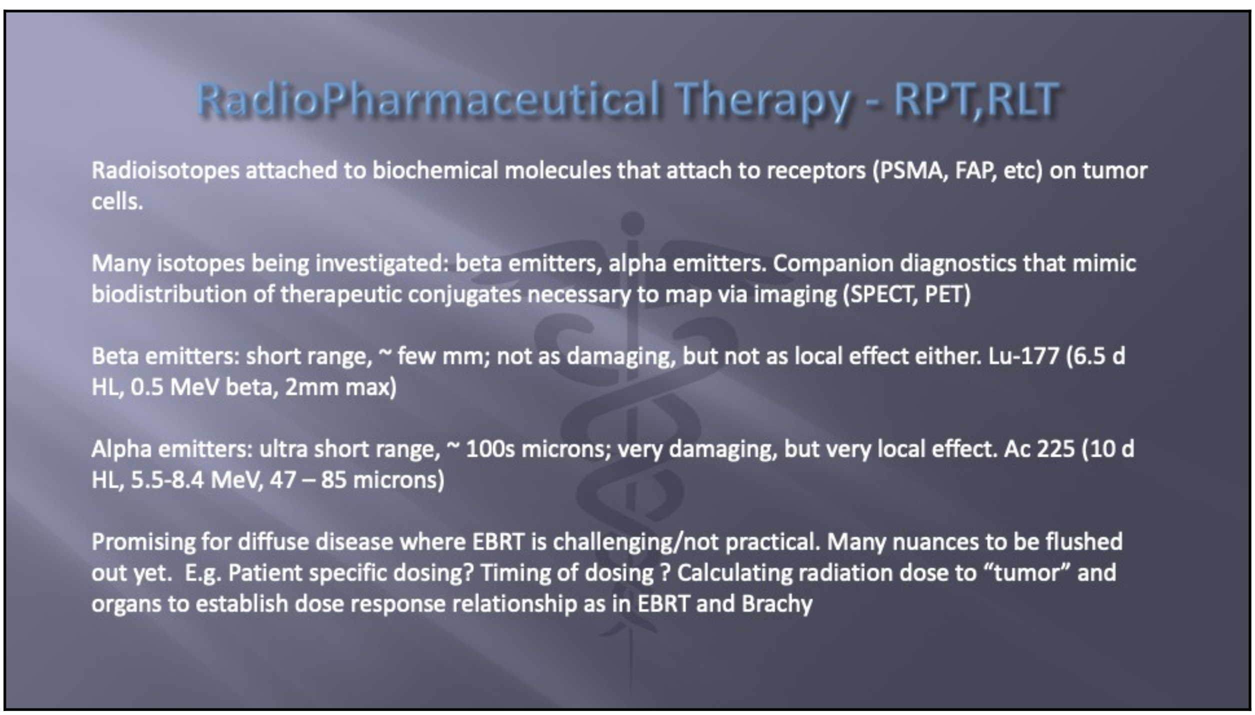

A few thoughts about brachytherapy. I don't know if it has been discussed with you. We do a lot of these procedures at my current hospital. It's not quite an operating room, it's a clean room, and the patient's under anesthesia. We use a rectal ultrasound with a Biplanar probe, so we can look at the prostate in two different cuts. Then we are able to put these needles and then insert the seeds very precisely, away from the urethra, and away from the rectum. We do a radiation plan on the fly in the OR (operating room) with the patient on the table. Then we insert the seeds. The procedure is complete in about 45 minutes to an hour, and the patients go home. Since this requires very delicate and accurate placement of seeds, it requires a lot more skill from a radiation oncologist than it does for delivering external beam radiation.

Unfortunately, the field is dictated by reimbursement issues. This used to be popular some time ago, but not as much anymore.

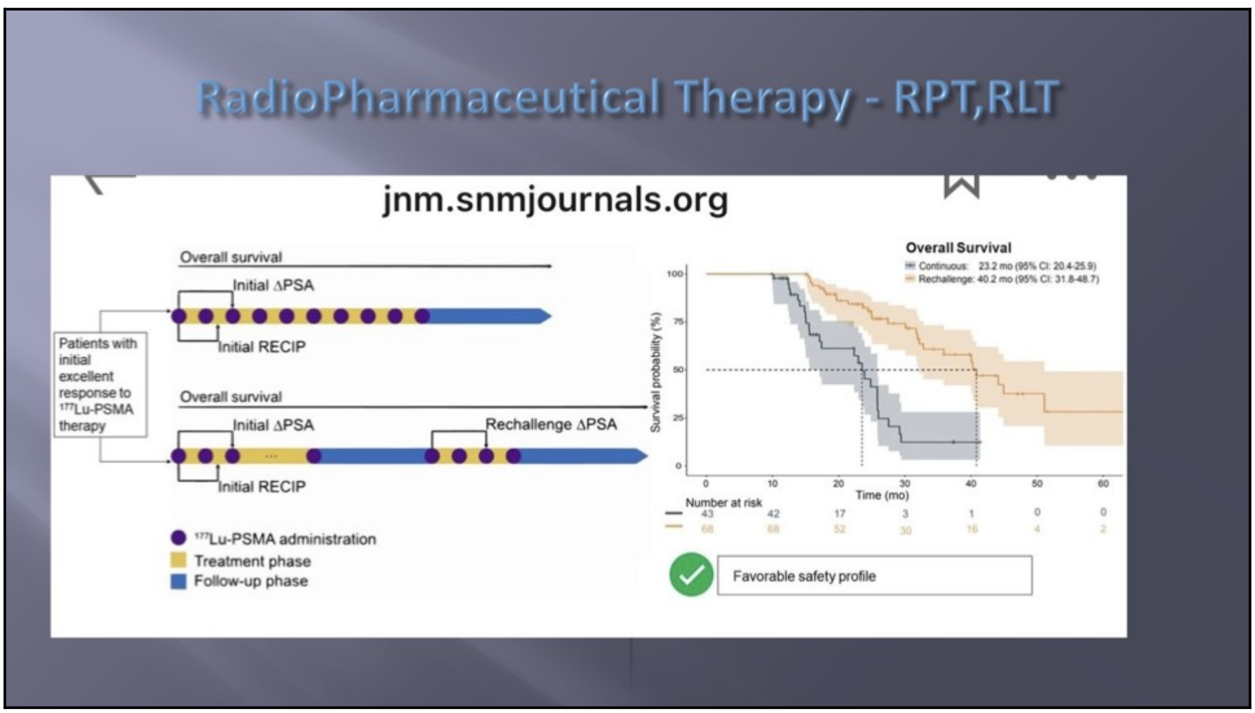
## “Navigating Radiation Treatments” (Chandra Kota, PhD) [#97]



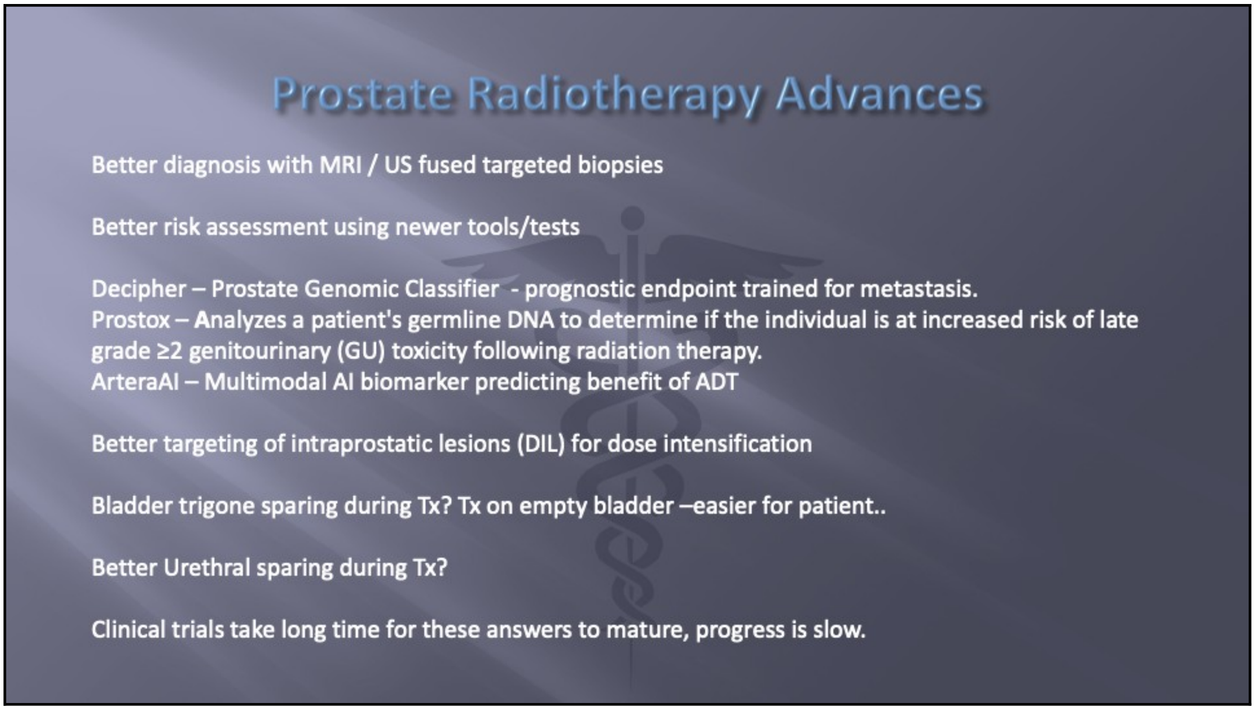

We use two different kinds of seeds: iodine seeds and palladium seeds. They have different characteristics. These are what we call dose distributions around the seeds. We have all these bright spots that you see on the CAT scan of different seeds. All these doses add up to create a composite dose distribution to treat the prostate to the desired dose to achieve good local control.



Radiopharmaceutical therapy is a very new and interesting development that's come about in the past few years where you have radioisotopes attached to biochemical molecules that attach receptors. There are more and more new receptors being discovered and investigated these days. The field is growing exponentially. There are two different kinds of emitters, current radioisotopes, that are being investigated as well, beta emitters, which are basically electrons emitted by isotopes, and alpha emitters. Beta emitters have a low LET (linear energy transfer), so they're a very diffuse kind of ionization ins. And alpha emitters are high, and it is a very dense ionization is the key step companion diagnostic. So you're able to assess ahead of time like where the RPT is radiopharmaceutical is going to go, and if it's safe enough to administer it to the patient. So the beta mettlesome, short range few millimeters, they're not as damaging, but not as local either. So they give radiation even to cells that are not immediately in the vicinity of the radio, pharmaceutical, alpha meters are much shorter range. In comparison, just a few hundreds of microns. They're much more damaging, but very local effects. So we need to make sure that there's enough of these isotope molecules close to each cell that you want to kill. So this is a very promising technique for diffuse disease where external beam is not practical or cannot be just done. There's many nuances to be flushed out like a patient specific dosing. Like right now it's unit dose for all patients timing of dosing. And the field is just beginning to try to figure out how to calculate radiation dose to tumor and organs and try to establish a response because an external beam radiation therapy and Reiki therapy, there's a long history of understanding the relation between radiation dose and tumor response. So it would be useful to have this so we can fine tune radiopharmaceuticals therapy a little better.




I just saw this on LinkedIn today. There's a study out of Germany showing that with leutetium they had, instead of the straight course, a gap in between, and they showed that they were able to get a better patient survival. These kinds of investigations are just beginning to happen now that the drugs are out and FDA approved.




A few advances in prostate radiotherapy that we see from the trenches.

There is better diagnosis with multi-parametric MRI and ultrasound-fused targeted biopsies. When you do a biopsy, you're hitting the area where you know where the disease is.

There's better risk assessment using newer tools and tests. We use these tests in our clinic:

- Decipher – Prostate Genomic Classifier - prognostic endpoint trained for metastasis.
- Prostox – Analyzes a patient's germline DNA to determine if the individual is at increased risk of late grade ≥2 genitourinary (GU) toxicity following radiation therapy.
- ArteraAI – Multimodal AI biomarker predicting benefit of ADT

For radiation treatments, we are able to target lesions that are more suspect for disease, instead of the whole prostate. Conventionally, we used to treat the whole prostate with a uniform dose. But now with multiparametric MRI, we can see the areas of disease more clearly. We incorporate that into radiation planning. We keep those areas at a higher dose than the rest of the prostate with hopes of controlling the tumor better.

Some of these, hopefully, will, in the near future, enable us to figure out how to spare more critical structures that we define more carefully instead of gross structures, such as the bladder trigone, and better urethral sparing.

Unfortunately, this is a well-established field, and to show that we can benefit patients, we have to be very careful and methodical in what we do. Clinical trials take a long time for these answers to mature because the side effects take quite a bit of time to manifest themselves. So it's not something we can do in a few months.


Chandra Kota 31:07
We have challenges in radiation therapy as a mature field.

There is little policy support for innovation. Our reimbursement is mainly dictated by CMS, and usually in a downward trajectory.

There's little incentive for private equity investment because of reimbursement issues, which is very different from the pharma field.

Research is conducted by institutional or cooperative clinical groups. It's not as well funded as pharma research.

Also, there is no marketing to educate the general public. Many patients are not aware that the radiation that we give today is not the same radiation that they might have heard about 20 or 30 years ago, which caused a lot of side effects to their loved ones.

Brad Power 32:08
Thank you for that overview.

I would encourage anybody who's had experience with radiation to share their stories, so that we can see it from the patient's point of view and maybe ask some questions, what treatment you had, and how things might be different today.

We've had sessions on radioligands. Oliver Sartor is a leader in this area. He had a session with us where he talked about this. That seems to be more in the pharmaceutical area because Pluvicto, in particular, has become a popular line of therapy. It has almost achieved blockbuster drug status. So at least the radioligands would seem to be getting the kind of investment that you said is hard to find when you're talking about machines, like big pieces of hardware that deliver radiation. So maybe there's a crossover there. Are you not seeing that the pharmaceutical companies are very happy to invest in the kind of radioligand types of therapies?

Chandra Kota 33:46
No. You're correct. Radioligands are pharmaceutical products. They're investing very heavily. Just in the last six months or so, there's been a lot of startup activity. Big Pharma has spent collectively like $10 to $15 billion buying different startups. So they're definitely betting big on radioligands. There's no doubt about it. I would very much hope that they work. But the problem is, we know that when you start targeting receptors, you might get most of the cancer cells, but all you need is a few left behind, and they start going back up again. So it's not a cureall or a solution that would solve the problem or enhance local control for everybody across the board for extended periods.

If you had those kinds of investments in external beam, for example, we would see a lot more innovation using other kinds of technologies. It's another kind of targeting. It's a different way of thinking about it. We might be able to achieve better control for a lot of patients.

For example, we keep complaining within our field that protons are very expensive. Again, that's related to the reimbursement issues. If we compare those treatments to what the radiopharmaceuticals cost, probably they're not relatively expensive. And if you start thinking along those lines, then maybe we can show much more value, with those kinds of advanced technologies, which cost a lot more.

Rob Weker 35:41
Let me share my patient perspective around radiation, because as a three-time cancer survivor, I've had radiation three times, so I can describe different journeys.

My first one, which was for testicular cancer, was back in 1991. At the time, it was probably very old technology that was used. Let's put it this way: the technicians would get me set, and then they'd go down the hall, and they'd run, and they would yell to me, “Hold your breath.” And the machine went on and did its thing. Then they would come back, and it was fairly archaic. It was an external beam, but I'm sure it was not very targeted, and not very focused.

Then in 2010, I had liposarcoma and had surgery followed by radiation treatment on my back, which was, I believe, four weeks of continuous radiation treatment. The interesting aspect of that for me was overexposure. To this day, I still have burns from that treatment. So again, external beam. I'll say fairly low technology at the time.

In 2015, I had proton beam treatment as a follow up for pancreatic cancer. So after Whipple and then chemotherapy, I had proton radiation. I'm going to come to the reimbursement aspect in a second, because that is a huge, huge challenge. But interestingly, the case that got me to have the insurance company eventually pay for the proton beam was that my radiologist argued that I'd had so much radiation exposure previously, that it really needed to be very targeted and as minimal as possible. That was the rationalization for using proton beam. We thought it would be more effective, but with traditional radiation, my body probably just couldn't handle that level of dosage.

But it raises an issue. I'll throw it out and more as a question, in terms of the whole reimbursement angle as it relates to proton beam: How do we go about making a more compelling case as a patient to have proton beam considered as a viable option versus the cheaper standard radiation approach?

That's a bit of background, and then a question.

Chandra Kota  39:11
Yes, without a doubt, protons definitely have a benefit. They're much more focused, and we can tailor them much better than photons. We see more and more patients coming back with other cancers or recurrences. This re-radiation is also new to us in our field. The science and the biology has to be fleshed out. We don't know how the tissues repair themselves, with all these different kinds of treatments that we've been giving. There's a renewed interest in that.

Going back to your sarcoma, that's a very difficult one to treat on the surface because we don't have as much control in terms of how we can define the radiation. Skin tissue is much more sensitive. One of the reasons for developing the megavoltage beams was that in the very old days, they used to do them with X-ray machines, and they could only do as much as could be tolerated. So they coudn’t treat deep seated tumors because skin would burn up first.

Chandra Kota  40:29
On reimbursement, my personal thoughts are that, I wish as a policy, we could say, if any treatment – it doesn't matter what treatment it is – creates a certain effect, if it gives you control for 10 years, regardless of what you do to get there, they should all be paid the same. That would be ideal. It doesn't matter if it's a drug, or if it's protons, or it's photons, and anything else one can think of, because the end result is really what should be driving the reimbursement. Unfortunately.

Rob Weker  41:02

I agree. I'm suspicious, and I believe my current oncologist is also suspicious, that my initial treatment with radiation for the testicular cancer caused the pancreatic cancer to develop 20 years later. I'm very sensitive to “the more targeted we can get, the better”. And if it can avoid these downstream issues. At the time, proton beams didn't exist. It wasn't really an option back in 1990. But by the same token, now, I would hope that if proton offered a better solution, and longer term more stability, that reimbursements wouldn't be the hurdle, the standard way.

Brad Power 42:03
We had a session with Carl Rossi of California Protons. You can see the notes and links from that session here.

Jeff Dwyer did research on different radiation centers. Even though he is based in the Boston area, he ended up choosing a proton center in the Philadelphia area. He was very complimentary of the Proton Center that he found in the Philadelphia area.

Chandra Kota 43:06
That would be UPenn.

The proton technology was developing so fast that not all proton centers have the same technology. There are some that are using older technology, which is where it doesn't define that proton dose as nicely, as a newer facility might be able to do.

WIth an MR Linac, with MR guidance, you can see what you treat. People thought that that machine could not be built. But physicists persevered, and they were able to figure out the technological hurdles and overcame them. I was reading recently in the new trade literature that people have started figuring out how to combine MR and protons. If you're able to see what you're treating with protons, that would be great, except the cost will be quite high, and you need to figure out this reimbursement piece in the whole grand scheme of things.

Allen Morris 44:18
You are a medical radiation physicist. You are not a radiation oncologist. You know a lot more medical radiation physics than a radiation oncologist. I just want to point out to everybody these two fields in medicine are not the same.
[AM editorial: This is one of my soapboxes:
The knowledge intensiveness of each of the sub specialties in medicine.
And a corollary of that soapbox:

And that if you have an understanding of the educational background and subsequent experiences of the experts before you, you can better direct the “conversation” or in this case questions in the learning session, to the “experts” wheelhouse, as opposed to getting their 2nd and 3rd language informed opinions. As a pathologist, I have arguably a 2nd language grasp of all of the fields in medicine, but if I were to answer questions better fielded by someone actually practicing decades in the issue at hand, one would get a beyond better informed answer, and in the case of not-known phenomena, best educated guess.

Though, you work intimately with radiation oncologists and thus, your knowledge transfer, working intimately together under the same roof, must be one of the closer of any two fields in medicine; you have orders of magnitude more knowledge of radiation physics than a radiation oncologist; because you majored in it, you got the diplomas to prove it, which you must display prominently to protect the public, institutions are required to credential you to allow you to practice, you have been practicing it for decades, and thus you additionally have gray hair experience. Accordingly, I do not want to ask you a radiation oncology question,
I want to ask you a medical radiation physics question.]

You pointed out in your planning that, for example, the historic conformal radiation therapy treatments had four beams. You also pointed out, that the newer IMRTs have six beams in a roughly circular configuration. Then you also showed, implying that it's more advanced, the volumetric arc, where it spins around the whole body. The main difference, among all of these is not the ability to target the lesion, but to minimize off-target toxicity. By doing this volumetric (VAMT) technique using many different beam angles, you're attempting to reduce the off-target dose. Is that correct?

Chandra Kota 46:35
Let me explain it a little differently. When we went from three dimensional to conform, like I mentioned, there was a piece of technology called a multileaf collimator. Unfortunately, my video didn't play, and I couldn’t show it. Imagine radiation, like a flashlight, pointing it at the tumor. This multileaf collimator is like little slivers of metal that move in and out of that flashlight beam, trying to create different shapes at the tumor. The earlier versions of multileaf collimators that we had could only work while, the gantry is what we call the machine, it was fixed at different positions around the patient. That's why we first called it IMRT. It was slow, because it had to go to a position at a patient. And then the leaves had to move, and you had to give the radiation, then you go to the next position, and the leaves had to move again and you get radiation. It does better than the 3D CRT, conformal therapy, no doubt. But it's not as good as a volumetric because now the gantry is moving continuously. Every one degree or so as we go around the patient, the shape of the leaves changes, and it conforms to the target more precisely. In some directions, let's say there's a rectum in the path, it blocks the rectum more. So you're also modifiable. We're also able to shape around the organs that you want to spare very nicely.

And it's fast. It's much faster than the older technology. So the patient may lay there just for like five minutes instead of 20 minutes, that they had to earlier. That helps a lot. Because I've seen patients, like prostate cancer patients, and we tell them to fill their bladder. It's very difficult, and it's stressful, unnecessarily. The faster we do these treatments, there's less movement of the patient once we set them up and image them, and we can give better treatments.

Allen Morris 48:31
You introduced two other variables: a collimater with metal leaves, that makes more precise shaping of the target area and reduces the off-target dose, and the speed of the machine. I

presume that makes the math of radiation physics even more complicated. That's why your field is a field because it's complicated. It requires higher math, physics, and other things that only a medical physicist knows in order to do the treatment planning and is beyond the working (practicing) knowledge of a radiation oncologist, otherwise you would have the same education, credentialing process, perform the same tasks, and would have the same experience.
[AM editorial: I am emphasizing that radiation oncology and medical radiation physics are two distinct fields.]

But nonetheless, even if you had an optimized collimater plan, and you had an optimized speed, would not optimizing the number of beam paths also help in reducing off-target toxicity?

I was surprised that in the proton treatment, all that is used is two (lateral directed) beams. Even if you accept that there is no exit bath, by virtue of the Bragg Effect, there is still an entrance bath. Would not four beams reduce the entrance bath compared to just the two from the lateral sides used in the proton beam planning image; for example adding an anterior and posterior beam path?

Chandra Kota 49:50
Operationally, that's an issue with throughput. If you only do it with two beams, you'll be treating more quickly. If those machines also got much faster, then they're able to deliver these proton beams at a higher rate. Then you can optimize the timing it takes to treat the whole patient. There's no downside to doing it with more beams. It just takes longer. Maybe those facilities feel that it's not clinically important to reduce it anymore.

Allen Morris 50:21
In other words, with your complicated math and physics, in combination with cost issues (e.g. insurance, workflow, patient on table discomfort), and who knows but a medical physicist how many other factors, the proton medical radiation physicists have optimized the proton therapy process, figuring out that two (lateral) entrance beams are good enough?

Chandra Kota
That's correct.

Richard Anders 50:58
Allen's very interesting point just made me wonder, what's the theoretical minimum if you had an infinite number of beams? It probably depends on the shape. But for an average non zero organ, is there a theoretical minimum of what radiation you can deliver off-target, and still give an arbitrarily high radiation to the target?

Chandra Kota 51:30
With photons, there isn't one. Like I said, photons go everywhere. With protons you could.

Richard Anders 51:39

WIth protons, you can deposit it exquisitely sensitively. In theory, you only need one beam to get it exactly where you want it.

Chandra Kota  51:49
You're just creating a pinpoint in the patient's body. You just need one beam. The Bragg Peak is very, very sharp. You'll be able to do it for a very small target. But where the target gets bigger, you need to be able to cover the whole target. And then the Bragg Peak effect goes away. It gets smeared out.
[AM editorial: Proton beam therapy still includes an off-target entrance bath, which I presume ideally should be minimized, if any radiation off target dose is considered undesirable as Dr. Rossi taught me in his learning session. *“Radiation is a toxin and there probably is no dose below which toxicity does not occur… Let's limit toxicity … by whatever technology we have to maximize target dose and minimize normal tissue dose.”* - Carl Rossi]

]

Richard Anders  52:09
Does the Bragg effect scatter in all dimensions? Or does it just keep going in a straight line?

Chandra Kota  52:15
It's a collimation. The Bragg Effect has mainly to do with depth. It's the distance for which the proton would travel.

Richard Anders  52:28
I see. So if you could assume that a beam travels in a straight line and scatters really more or less in a straight line, and you had an arbitrarily large number of beams …

Chandra Kota  52:40
Like for the prostate the cross section, maybe like four or five centimeters. So the beam would be four or five centimeters across, that's directed at the prostate.

Richard Anders  52:56
And you can deliver, in theory, arbitrarily high doses to the prostate and arbitrarily low doses out of the prostate, if you had enough beams and enough time?

Chandra Kota  53:11
There will be a minimum, like you said. If none of the entrance beams are overlapping with each other, if they were all completely separated from each other, then the minimum would be, what's the entrance doors relative to the Bragg Peak doors? That would be the minimum target, but usually, because of the size of the target, the beams end up overlapping.

Richard Anders  53:35
Do you know anything about, and do you think that this is fertile ground, radiation sensitizers? I've seen a number of ideas for a drug here or drug there that will, in theory, home in

somewhere and then make it very sensitive to radiation? Do you think there's merit in that? And is that coming of age?

Chandra Kota 53:58
It's been the Holy Grail. You want to find something that sensitizes to radiation, so you can treat there. A very long time ago, I did my dissertation on something called boron neutron capture therapy. I'm seeing a little bit of activity there. So the idea was that like thermal neutrons, the boron has a very high concentration cross-section for thermal neutrons. If you're able to tag something that goes to the tumor with boron and then just sits there, and then you just bathe the patient with thermal neutrons, the differential is like 1004 for two tumors. It's enormous.

The problem is you just can't get the boron to go where you need it to go and nowhere else. But there is one startup company out in California, I think called T Life Sciences, which is doing something more on this. They're trying to ride the coattails of the radiopharmaceuticals activity going on. It's kind of related, but not quite the same.

Richard Anders 55:06
So there's nothing there that you think is ready for primetime?

Chandra Kota 55:10
There are a few radiosensitizers that we use in the clinic, but there's nothing that's substantial – nothing that creates a therapeutic ratio of a factor of two or something.

Brad Power 55:21
We have had some discussions of alternative therapies. One of the things we were talking about was hyperbaric oxygen, that was sensitizing people or potentiating the radiation more. Have you heard of that?

Chandra Kota 55:38
That's one of the reasons we fractionate radiation. Conventional wisdom was that we would kill off the tumor cells that were well oxygenated. And the ones that were not, that were hypoxic, would then get reoxygenated. Giving them in daily fractions helped in that regard. But when we went to giving very high doses, per fraction and a few fractions, like the so called SBRT, or stereotactic radiosurgery, there is not much going on even with the hypoxic cells. That pretty much kills everything.

A lot of biological mechanisms are still not very well understood. We keep talking about radiation killing cells, but those cells that die release all kinds of chemicals into this microenvironment that kills other cells. It's a very complicated phenomenon. So we're not quite sure. But on a practical daily basis, we do not do hyperbaric treatments before treatments. It's not practical.

Brad Power 56:45

What is the role of the medical physicist in evolution? So let's just say we've been talking a lot about prostate cancer, maybe a patient got a prostatectomy, and then they're going to radiate the bed to make sure they got all of it. What would your role be then in working with a radiation oncologist to define the plan?

Chandra Kota 57:14
In terms of expertise and education level, we are on par or next to the radiation oncologists. We directly perform or work with radiation oncologists in the most complex procedures. And for the less complex, and the more common ones, we oversee those procedures.

So for example, tomorrow, I'll be in the clinic doing three seed implants with my doctor. That's fairly complex, and it needs a lot of physics inputs. I'll be there with the patients and treating them. There's also a machine called CyberKnife, which delivers very precise high dose radiation. In that line, the physicists are involved in doing the planning and the treatment as well. But if you were to get a conventional prostate treatment, like 30 fractions, 30 treatments or so, we would not be at the machine doing it, or we would not be doing the plan directly ourselves. We would have the dosimeters do the plans, and the therapists deliver the treatments, but we are overseeing the whole quality aspect of everything to make sure that nothing's missed, and everything's correct.

Allen Morris 58:37
People that don't live in the world that Dr. Kota and I live in; don't know how complex and what a beehive it is. You asked, Dr.Kota, “What's the difference? What are the different roles for radiation oncologists versus medical radiation physicists?” Dr. Kota brought up that there are all these other people like radiation therapists, dosimeters, radiation safety officers, biomedical engineers, aids of various flavors and educational levels, including insurance and billing personnel, that all are integral in delivering radiation therapy.

It's the same thing in laboratory medicine. We have a whole cadre of people that are involved in Clinical Chemistry, Blood Bank, Microbiology, Histology, Cytology, Hematology, phlebotomy, specimen processing, accessioning aids,  Physician assistants, etc. all requiring various levels of education and expertise. Like Dr. Kota, for most tests I'm not directly involved, but likewise I provide quality oversight. The people have all sorts of titles that go all the way from aids, to assistants, to technologists, and to clinical laboratory scientists, including people that have PhDs, so they are doctors also, just not medical doctors.

I'm on my soapbox concerning the Tower of Babel. All these specialized fields, even within what you might think is a unitary specialized field such as radiation oncology or pathology/laboratory medicine have many different role players with varying educational backgrounds and credentialing paths, within them.

Dr. Kota was asked about radiosensitizers, and he said. “That's the Holy Grail. We don't know.” There's an avalanche of preclinical studies including cell line and animal model studies with all these promising agents, but everybody's forgetting the elephant in the room, regarding prostate

cancer treatment. The elephant in the room is ADT. There are innumerable positive phase 3 studies, the proof in the pudding, that ADT combined with radiation therapy is synergistic. It not only is established, but is continuing to mature. For example, parsing patients into different risk categories for deciding not to use or on the other hand, if to use, for what duration, and with what flavors of ADT to use (e.g. monotherapy or double blockade and with what particular agents), and whether to do hormone therapy neoadjuvantly or concurrently. These ADT treatment nuances are maturing, continuing to be further refined, and are in guidelines.
ADT, something that has already proven to synergize with radiation therapy and thus by, at least loose definition, is a radiosensitizer, is here, and its usage, through research, continues to be optimized.

[AM editorial - Remember:  The highest level of evidence is meta-analysis of many randomized controlled trials. That highest level of evidence can only be found within a maturing concept over time after many randomized controlled trials all point in the same direction.  My suggestion: if you are thinking you want to explore “frontier” radiosensitizers, by all means, but regarding prostate cancer, you should start with tried and true, ADT. And note in this upfront context, it is not for life, it is for synergy with Radiation therapy, and thus of finite duration.]

Rob Weker  1:01:40
Can you comment on flash proton technology?

Chandra Kota  1:01:56
It's definitely in preclinical. They've seen that it does something very different than what we're used to in terms of what radiation does. So it goes back to the fact that it seems to do different things at different dose levels and different dose rates, and we are still trying to understand what it does. I guess you'd be able to translate it into a clinical pathway.

Chandra Kota  1:02:25
As a field, we could use more patient advocates. Those who have had good experiences should speak up on our behalf, maybe with their friends and families, so that people are not scared of radiation and realize that it has a good role to play.