## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]

Brian McCloskey, Allen Morris, and Brad Power
May 15, 2023

*“The cancer cells could care less what you're hitting them with. They don't know protons versus X-rays. It's what you do or do not do to the surrounding tissue that makes the biggest difference.”* – Carl Rossi

*“If you can identify a target, which means your imaging is showing you something, you want to hit it harder.”* – Carl Rossi

*“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

**Meeting Summary**

Advanced cancer patients face enormous challenges in eradicating their metastatic lesions, especially when their cancer has spread to several different locations in the body, hard to reach locations due to proximity to vital organs, and tough body parts like bones or the brain. They can consider surgical removal and various kinds of radiation. The disadvantages of surgery include: inability to kill microscopic disease around the edges of the tumor, which may leave tumor cells in the patient after surgery, and difficulty in tolerating the surgery and anesthesia (i.e., they must have minimal medical problems, good lung function, and not be on certain medications).

Traditional radiation delivers X-rays, or beams of photons, to the tumor and beyond it. This can damage nearby healthy tissues and can cause significant side effects. By contrast, proton therapy delivers a beam of subatomic particles that stops at the tumor, so it's less likely to damage nearby healthy tissues. Most commonly, proton beam therapy is used to treat tumors near critical organs or structures, such as head and neck cancers, and increasingly in spine, breast, sarcoma, brain, and prostate cancers. This is particularly beneficial to those who are vulnerable to radiation or have received prior radiation either to or immediately adjacent to the area that needs to be treated. Proton beam radiation therapy may be safer and just as effective as traditional radiation therapy for adults with advanced cancer.

Proton therapy is generally more expensive than traditional radiation, and not all insurance companies cover the cost of the treatment, given the limited evidence of its benefits. Nevertheless, over 40 medical centers, including such NCI flagship institutions as Memorial Sloan-Kettering, Mayo Clinic, and Johns Hopkins have spent millions of dollars building proton therapy centers, and many advertise the potential, but unproven, advantages of the treatment.

Carl Rossi, MD, and Medical Director at California Protons, is uniquely qualified to discuss the issues and solutions in proton radiation. Dr. Rossi has personally treated more than 13,000 prostate cancer patients with proton radiation over the last 31 years—more than any other physician in the world. Internationally recognized for his achievements in cancer treatment, Dr.

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Rossi is a radiation oncologist with a research focus on the quality of life and cure rate in prostate cancer and lymphoma. Specializing in proton beam therapy, he has been treating prostate cancer patients with proton therapy since 1991. Prior to serving as the Medical Director of California Protons, he was the Medical Director of the Scripps Proton Therapy Center and was an Associate Professor in the Department of Radiation Medicine at the Loma Linda University Medical Center. He is currently also a professor of radiation medicine on the UCSD Radiation Medicine faculty.

Dr. Rossi gave an overview of proton therapy for prostate cancer and a summary of recent papers. He discussed success stories in prostate cancer, why to choose proton therapy vs. alternative radiation approaches, and when proton therapy works/doesn't work.

**Key Take-aways**

- The target for radiotherapy is DNA. With any type of radiation you are causing DNA breaks. The idea is that you create enough breaks to overwhelm the cell's ability to repair that damage, so the cell dies when the cell attempts to replicate. Normal tissue is somewhat better at repairing this versus malignant tissue. But that difference is often not that great. You try to target specifically because the more dose that can put in the bad stuff, the greater you can crack that window open. Unfortunately, the repair difference between bad tissue and good tissue is small. Radiation is a toxin, and there probably is no dose below which toxicity does not occur.
- To be able to hit what you're aiming at you need a good idea of the target, which depends on getting multiple images from multiple technologies, such as CT (computer tomography, which uses X-rays to create a 3D picture), MRI (magnetic resonance imaging, which uses magnetic waves), and PET (positron emission tomography, which uses radioactive substances to visualize; PSMA PET scans are used to view prostate-specific membrane antigen cells in prostate cancer) scans. Some cancers, such as prostate cancer, uterine cancer, and certain liver cancers, are pretty much invisible or very hard to detect on a CT scan.
- If you compare the standard X-ray (Intensity modulated X-ray therapy) therapies and proton radiation therapies in prostate cancer, you create a lot less toxicity using protons because you aren't hitting the intestines with radiation when you are using protons. Proton patients had secondary cancers at less than 1/3 the rate that was seen with other types of X-ray therapy.
- The higher the dose you can give, the lower the probability of either local failure or failure elsewhere in the body.
- Pencil Beam proton radiotherapy is effectively a 3D printer. You're painting the dose in layers, a millimeter thick, through your target. You can put high doses in some spots, and lower doses in other spots.
- Particle therapy is no longer a boutique treatment that is only available in one place or two places in the world. Different manufacturers are making the machines, including companies like Hitachi, and as a consequence machines are becoming less expensive. The cost for proton treatment is getting closer to the cost of X-ray (IMRT) therapy.

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- Despite the advantages of proton therapy described above, IMRT is still and will be for the immediate future the standard of care due to limited access of proton facilities; limited acceptance by insurance companies, specifically the cost disadvantage; limited head-to-head study comparisons with IMRT; and limited urologic community acceptance and public awareness.

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#### Meeting Notes

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#### Discussion Outline

- Dr. Rossi introduction. 0:00
  - Dr Rossi is an expert in proton therapy and all matters related to radiation oncology.
  - When does it make sense
- Radiotherapy and treatment of metastatic disease. 2:56
  - Treating solitary metastasis or a few metastases.
  - Target for radiotherapy is dna.
  - Empirically, radiation is a toxin.
  - Radiotherapy delivery technologies and radiation physics.
- Radiological use of fast protons. 8:29
  - The role of protons in delivering radiation.
  - Radiological use of fast protons.
  - Making proton therapy more accessible with smaller facilities.
  - New 3D printing technology.
- The importance of multimodality. 13:12
  - Importance of multimodality imaging in prostate and other cancers.
  - Prostate and pelvic lymph nodes.
  - Recent published data on treating intact Proton-based prostate cancer.
  - Comparison of proton and hormonal therapy.
- Proton vs. Imrt. 18:51
  - Treating the pelvis in prostate cancer.
  - Treatment of lung cancer with 3D-conformal x-ray therapy and imrt.
  - Intra-prostatic boosting for metastatic prostate cancer.
  - Red line patients with vocal boosts.
- Hormonal therapy vs. Stereotactic radiotherapy for prostate cancer. 25:19
  - Hormone therapy and stereotactic radiotherapy for prostate cancer.
  - Progression-free survival with hormone therapy alone.
  - Prolonged normal serum testosterone and quality of life.
  - Proton therapy for heavily pretreated prostate cancer.
- How do you get an ablative dose into the spinal cord? 30:40
  - Treatment of the T6 vertebral body.
  - Cost of particle therapy is becoming more expensive.
- Proton therapy and prostate cancer risk. 33:21
  - Higher doses of radiation are important.
  - Dr Rossi's case study with MRR.

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  - Tolerability of proton-based therapy to lumbar spine and thoracic spine.
  - Toxicities of VMAT vs proton therapy.
- Proton therapy vs. MRI-guided radiotherapy. 39:30
  - New endocrine component of prostate cancer.
  - Proton therapy vs MR-guided radiotherapy.
  - Cost of proton therapy for prostate cancer.
  - Cost of imrt vs 3D conformal.
- Do we have any head-to-head clinical trials of MR guidance vs. proton therapy. 44:59
  - No head-to-head trials yet on MR-guided linac vs proton therapy.
  - Advantages of MR-guidance vs ct-guided
  - Ionizing radiation for imaging.
  - Salvage treatment of the prostate bed after recurrence.
- Differences between protons vs. x-rays in treatment. 49:12
  - Comparing proton plan to x-ray plan.
  - Proton vs x-rays for pelvic lymph nodes.
  - Is proton beam therapy being used for bone marrow transplants.
  - Why protons are used in pediatrics.
- Diet and Radiation side effects of consolidation. 53:36
  - Ketogenic diet for prostate cancer.
  - Research on diet to mitigate radiation side effects.
  - No GI toxicity during the treatment.
  - Dr. Rossi, thank you for being my doctor.

## SUMMARY KEYWORDS

proton, treat, patients, radiation, radiotherapy, dose, proton therapy, toxicity, prostate, rossi, X-ray, treatment, people, therapy, bone marrow, cost, high dose, prostate cancer, marrow, intestine

## SPEAKERS

Carl Rossi (79%), Brian McCloskey (7%), Jonathan Starr (3%), Amit Gattani (3%), Jeff Krolick (2%), Kerri (2%), Allen Morris (2%), Richard Anders (1%)

## MEETING TRANSCRIPT

Brian McCloskey 0:00

I am happy to announce that Dr. Carl Rossi is here with us today. I just met with him last week regarding my own case, and the use of proton therapy, in my particular disease setting. Dr. Rossi is an expert in proton therapy and all matters related to radiation oncology. I've valued his counsel not only in radiation, but on how to navigate some of the challenges that I've had with my disease.

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Dr. Rossi came from Loma Linda University Medical Center, which is where I believe proton therapy was invented back in the 70s if memory serves me correctly, and he mentored with the best.

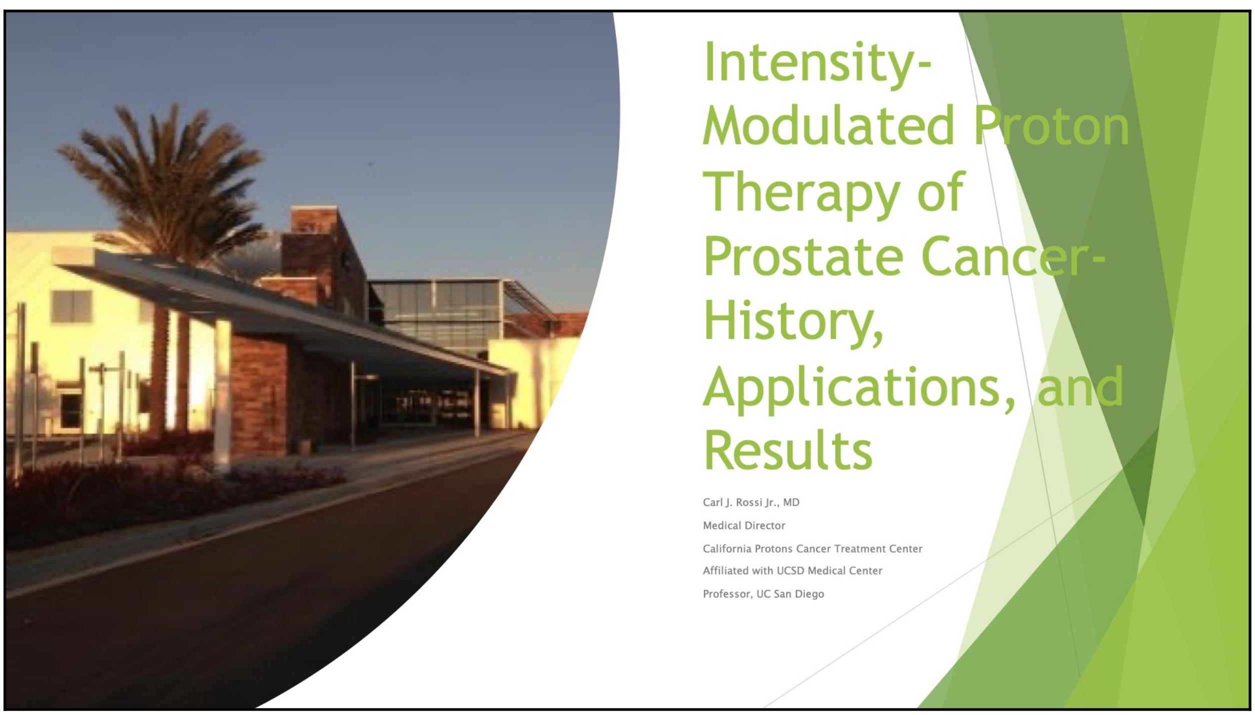
Dr. Rossi, If you want to add some more context, I think it would be helpful.

But before you do that, the main point for our patients is that when they're considering local therapy, it's often just a decision between doing surgery or radiation. Dr. Rossi is going to help us understand when that makes sense, and what is the difference between proton therapy and various other forms of local radiation?

Carl Rossi 2:12

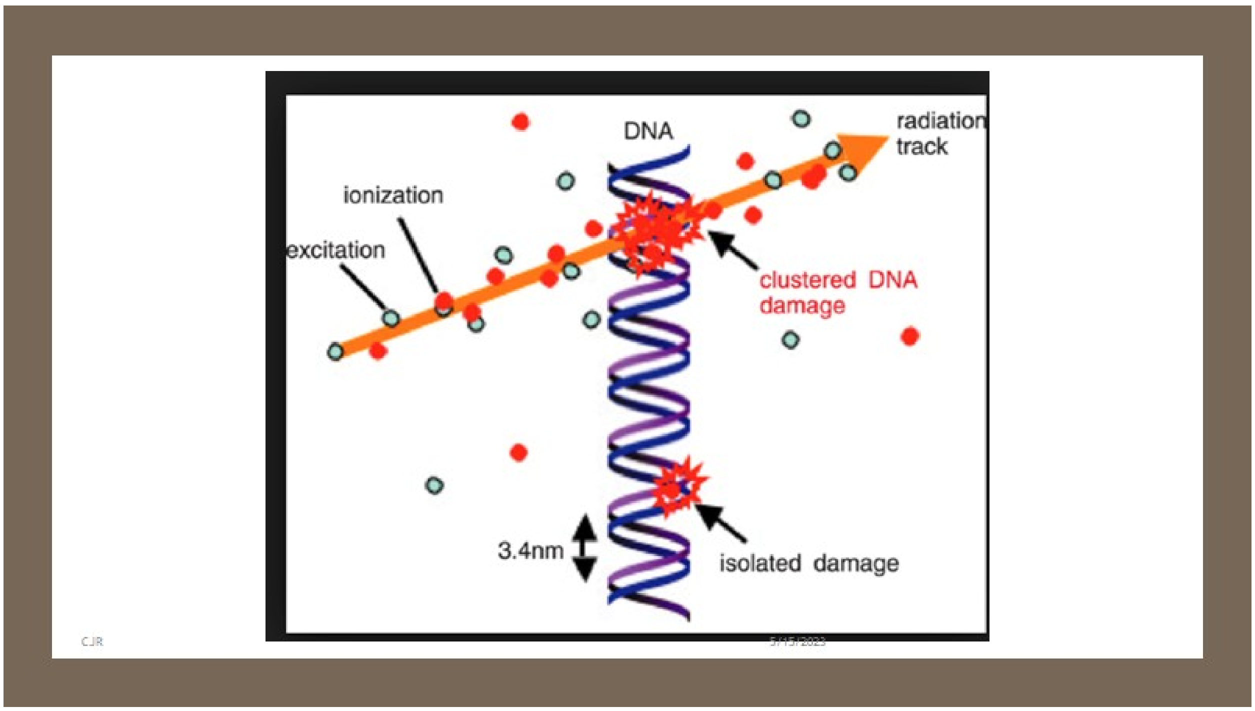
**Dr. Rossi’s history as a Radiation Oncologist**

I got into all this entirely by accident. I just happened to do my radiation oncology residency at Loma Linda, when they were starting construction of what was and is the world's first medical proton center. So I was there really by accident when everything was going at that place, and ended up staying there for almost 25 years. Then I came down here to San Diego when this facility was being built because of the technology differences, which are true now of all the newer centers, and I'll be touching on that again in this presentation.




Carl Rossi 2:56
There is going to be a fair number of slides. I'm going to go through them fairly quickly, though, because I want to save a lot of time for Q and A. I'm going to talk about the use of protons near

the end, both in primary therapy, it's one of the many ways to cure prostate cancer that's localized, and also in what we're doing more and more of now, which is treatment of oligometastatic disease. That's because we're becoming somewhat not victims, but it's a consequence of our success at controlling prostate cancer and other cancers. This idea of treating solitary metastasis, or a few metastases, really came about because the primary therapies and the systemic therapies have gotten better and that people live long enough to develop these problems which wasn’t as much of an issue even 10 or 15 years ago. So, it's in some respects a good problem to have until we get to the point that we can eliminate this stuff by radiotherapy and current therapies entirely.




**Molecular target of action for Radiotherapy: DNA**

Just to remind folks, the target for radiotherapy is DNA. That's what we do with any type of radiation. What we're doing is we're causing DNA breaks. The idea is that you create enough breaks to overwhelm the cell's ability to repair that damage, so the cell dies when the cell attempts to replicate. Normal tissue is somewhat better at repairing this versus malignant tissue. But that difference is often not that great. And that's why when you talk about radiotherapy, we've done a lot of things to try to be more target specific because the more dose we can put in the bad stuff, the greater we can crack that window open. Unfortunately, the fact is the repair difference between bad tissue and good tissue is small.

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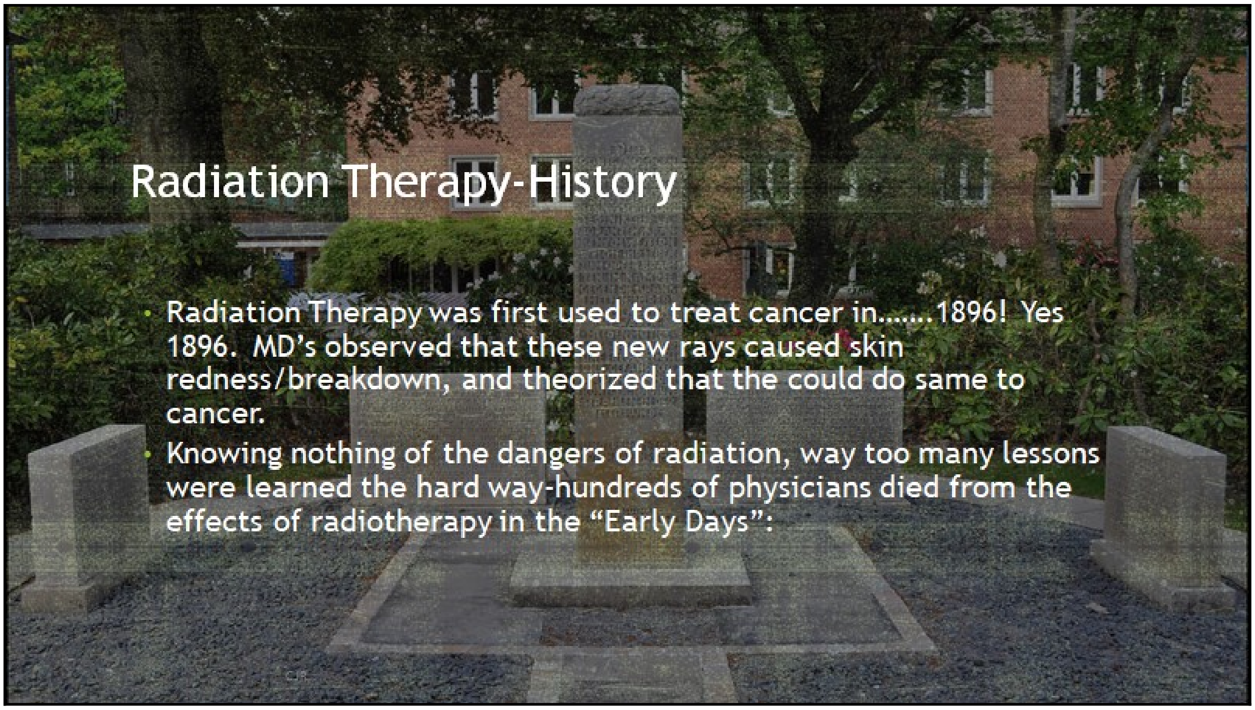


We've had radiotherapy for a really long time.

The most toxic mechanism of action of radiotherapy is double stranded DNA breaks. [Comment from Allen Morris: One does not want to create double stranded DNA breaks in normal tissue or a genomically stable indolent cancer because of the side effect: secondary cancers of normal tissue or genomic evolution of a stable cancer, barring “nuclear bomb”, ablative effect to the latter. One only wants to cause double stranded DNA breaks in an advanced cancer where “synthetic lethality” is operational, barring ablative effect.]

**History of Radiation Oncology**

It's been well over 100 years since it was first used in a very rudimentary way before the beginning of the 20th century. Within a year of the discovery of X-rays and natural radioactivity, people were using it to treat all sorts of stuff. They learned a lot of things the hard way. To illustrate, here is a picture of a monument in Hamburg, Germany to the radium martyrs, the several 100 people, clinicians, and other folks who died because of radiation induced diseases they developed. We learned the hard way, like so many things in medicine and in science. [Allen Morris: Marie Curie died from radiation-induced secondary leukemia, 1934; Rosalind Franklin, who did x-ray crystallography revealing DNA structure/existence, before Watson and Crick, an unsung DNA hero, died of “abdominal” cancer.]

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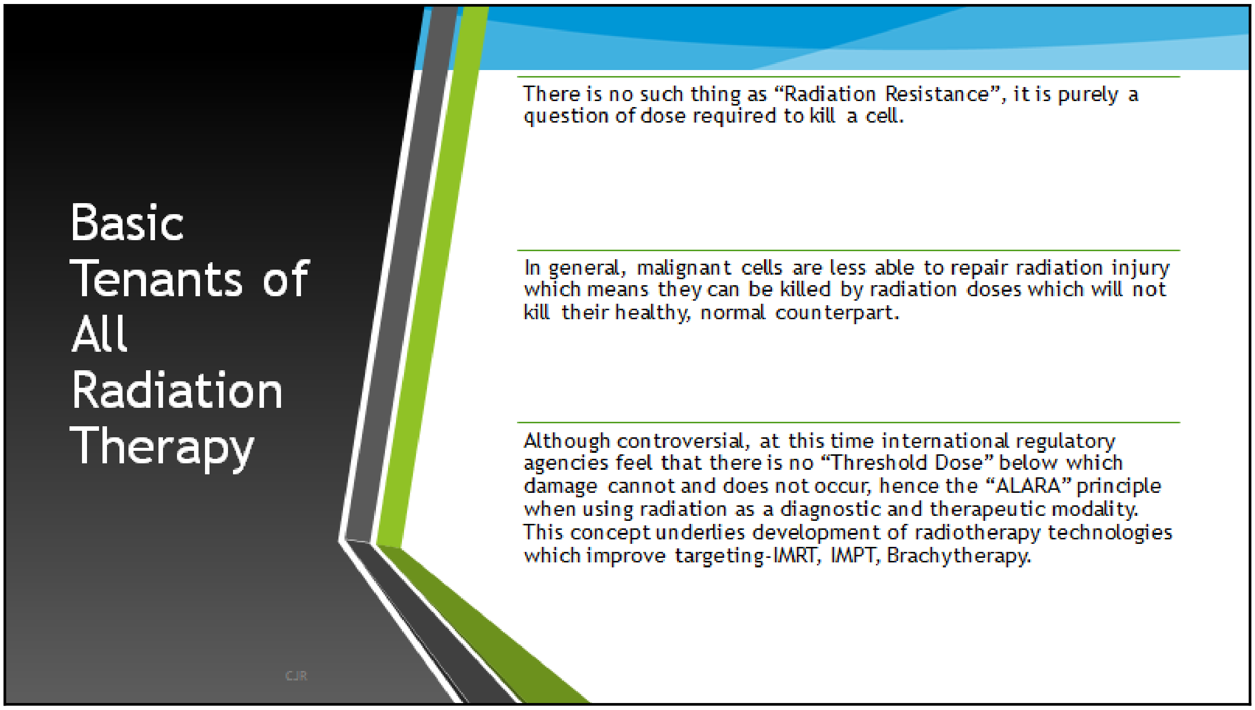


So we have some basic tenets in radiotherapy. The first is that nothing that we know of is radiation-resistant. Some things are more resistant than others. But if you give a high enough dose, you can kill anything with radiation that we know of. In general, the malignant cells, as I mentioned earlier, are less able to repair that damage, but that difference can be relatively modest. And the other is this idea that, learned empirically, radiation is a toxin, and that there probably is no dose below which toxicity does not occur.

**Off Target Toxicity (Organs at Risk/OARs)**

Certainly the higher doses are more toxic, but it doesn't mean that lower doses are non toxic. We have this concept called ALARA, an acronym for “As Low As Reasonably Achievable”, that underlies all radiation protection. Whether you're working in a nuclear power plant, or whether you're doing radiation therapy, or diagnostic work, we try to keep the dose to people as low as we can. And this is underlying all of our modern radiotherapy delivery technologies; this desire to spare people from unnecessary radiation.

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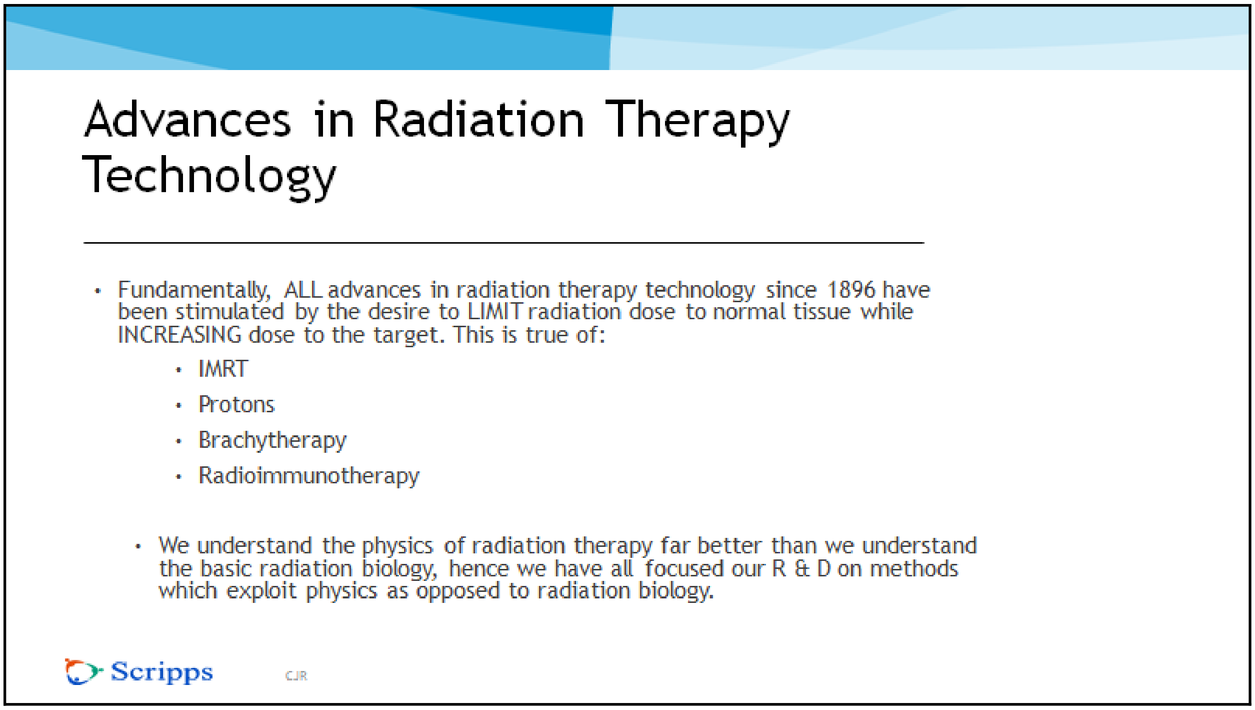


We’ve had a lot of advances. “Intensity modulated X-ray therapy”, “IMRT”, is probably the standard way (standard of care) of doing great X-ray therapy. We have protons, brachytherapy, or implants, and radioimmunotherapy, as many of you have experienced personally. These are all different variations on the same theme. That is, let's limit toxicity by being as careful as we can. Using whatever technology we have to maximize target dose and minimize normal tissue dose. The reason we all pull on the physics lever is because we understand it better. We do not have as nearly an accurate grasp of Radiation Biology, despite having studied this now for a long time, as we do on radiation physics. So we use the tool that we can exploit and that's the physics tool.

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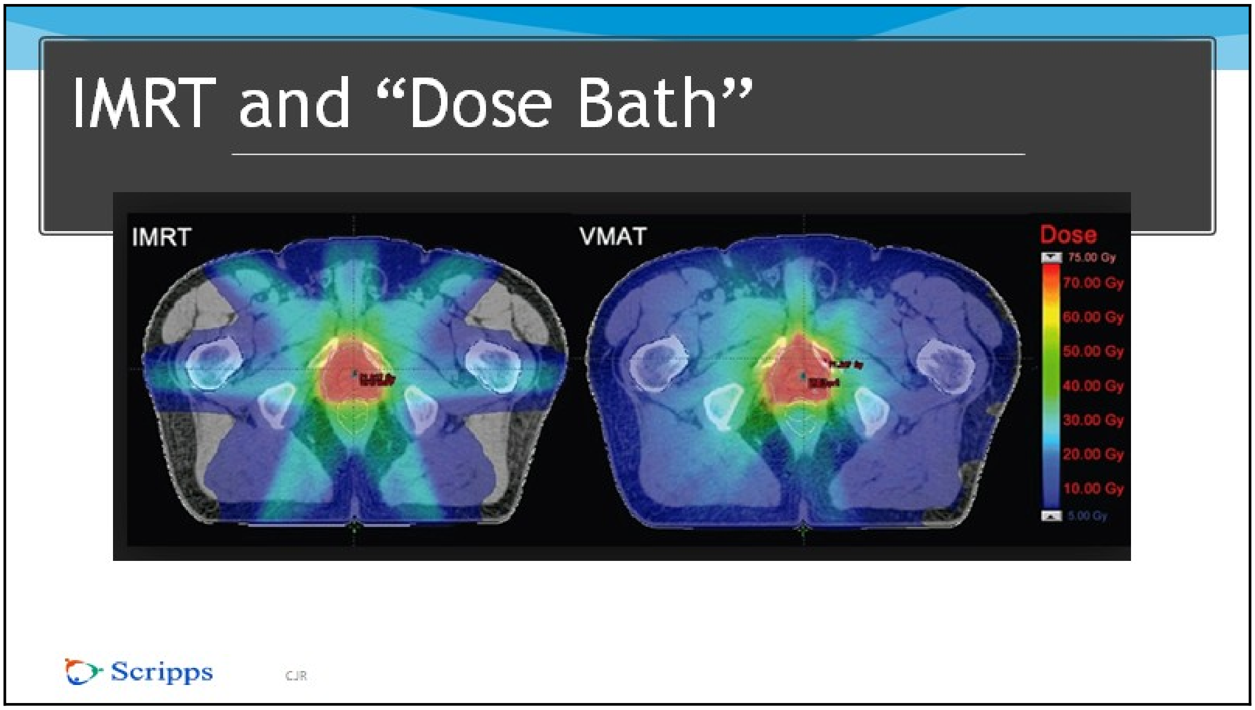


I mentioned a minute ago that IMRT is the standard radiation tool (standard of care). In IMRT you're using different X-rays, either in what's called a step and shoot fashion or arc, you're doing a volumetric arc, and you're varying the intensity of the beam as you deliver it so that you're stacking the dose, the highest dose to whatever target you want to hit. IMRT works great compared to three dimensional X-ray therapy of 10 to 15 to 20 years ago. But the problem is you're using X-ray beams and you have to dose on the way in and dose on the way out. So the compromise you have to make, if you're doing say IMRT to the prostate, is that they get this beautiful high dose to the prostate, but you're gonna give a bath of dose to everything else [Off target dose - Organs at Risk/OARS].

**The Radiation Bath**

People will say, “Well, it's low dose.” You have got to put that in context. When you are giving 8,000 rad to the prostate, you are unnecessarily giving 3000 rad to the intestine, and that's not a low dose. In fact, that's a very high dose to normal tissue. But when you're using X-rays, this is what you're stuck with from the physics side, because you can't make the X-ray beam stop at a point in space.

[Allen Morris comment: For perspective, diagnostic CT toxic radiation exposure is a concern. Diagnostic CT exposure to organs is on the order of 10 -20 milliGrays; <1/1000 the IMRT dose to the intestines cited by Rossi, above. Note Rad to Gy conversion factor: rad = .01 Gy. https://doi.org/10.1038%2Fs41598-021-85060-5].

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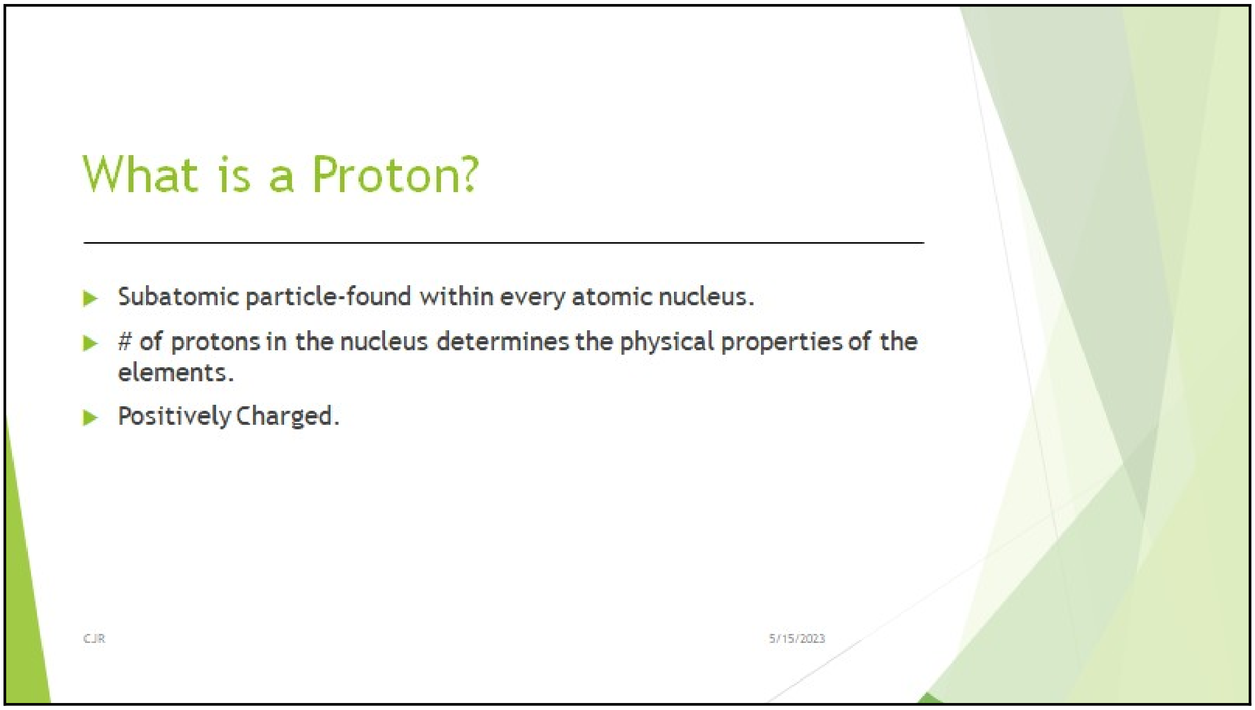
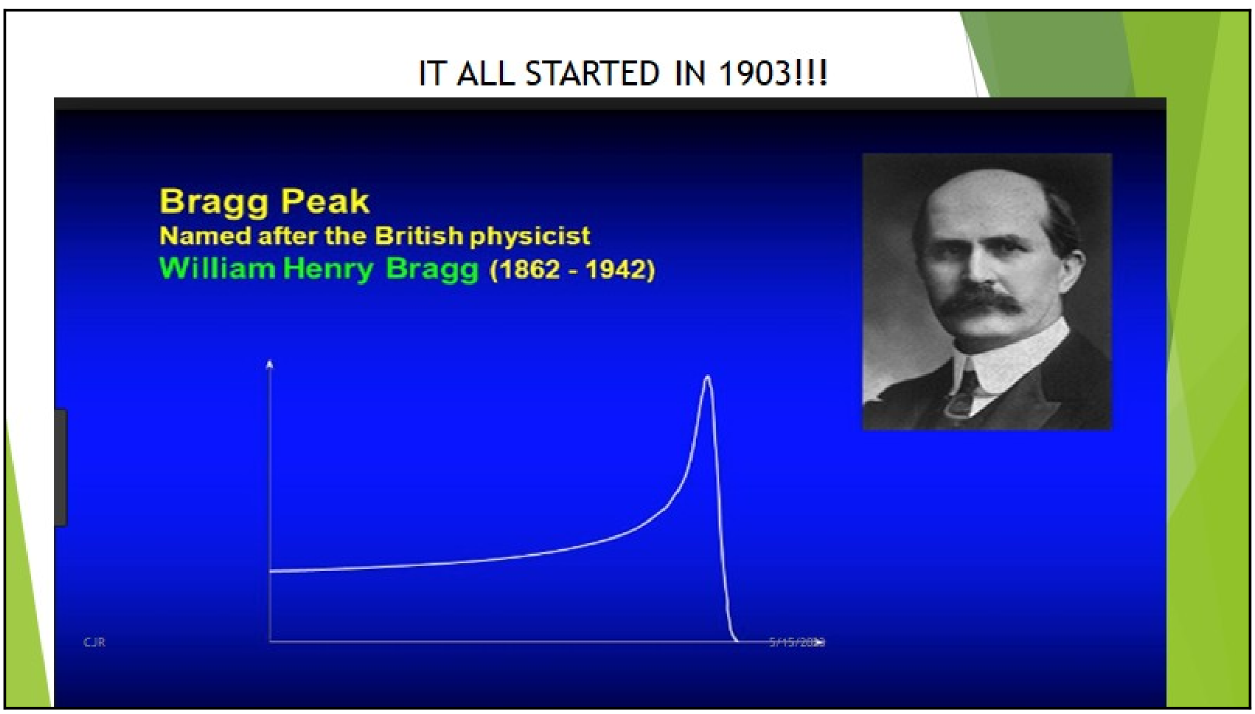



**Protons have a radio physical advantage**

This is where protons come in. Protons, as you know, are part of every nucleus. They have a positive charge. The number of protons in the nucleus determines the physical properties of the element [as in Mendeleev’s periodic table of elements].



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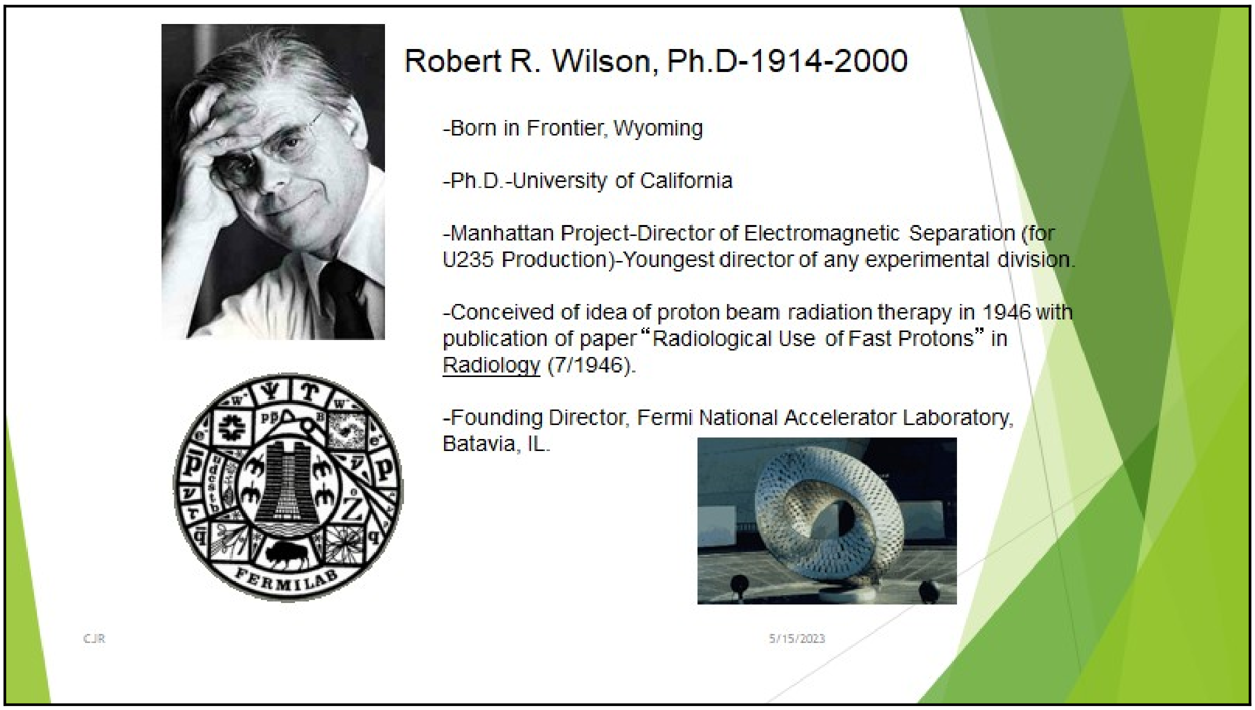
What all this means is that if you shoot them into things, there is ionization energy released. The proton radiation beam is not like that X-ray beam where the beam goes all the way from one end to the other. You have a point in space where the proton, a heavy particle, is coming to a stop where you get a spike of ionization energy and then the dose drops to zero afterward because the particle has come to rest.

[Allen Morris comment: As opposed to an X-ray (IMRT) which is a photon, a massless waveform that passes through the human body; thus hits all organs in its path].

**History of Proton Radiation Therapy**

This was discovered by William Henry Bragg, a Nobel Prize winning physicist of the early 20th century, in 1904. This is memorialized as the Bragg Effect (Peak).




But it wasn't till 40 plus years later that somebody said, “Hey, you know, that may actually be of practical use.” The person in question. Robert R. Wilson, a fascinating man who was the youngest section head at Los Alamos during World War II, did all sorts of other exciting and interesting things in his career. But in July of 1946, he published a paper called radiological use of fast protons in which he said, “Hey, perhaps if we could figure out how to stop these particles, decreasing off-target toxicity, that would be incredibly beneficial to patients, especially a brain tumor patient.” We could deliver radiation at depth without having to treat nearly as much normal tissue. And like most things in science, the concept occurs before you can actually do it.

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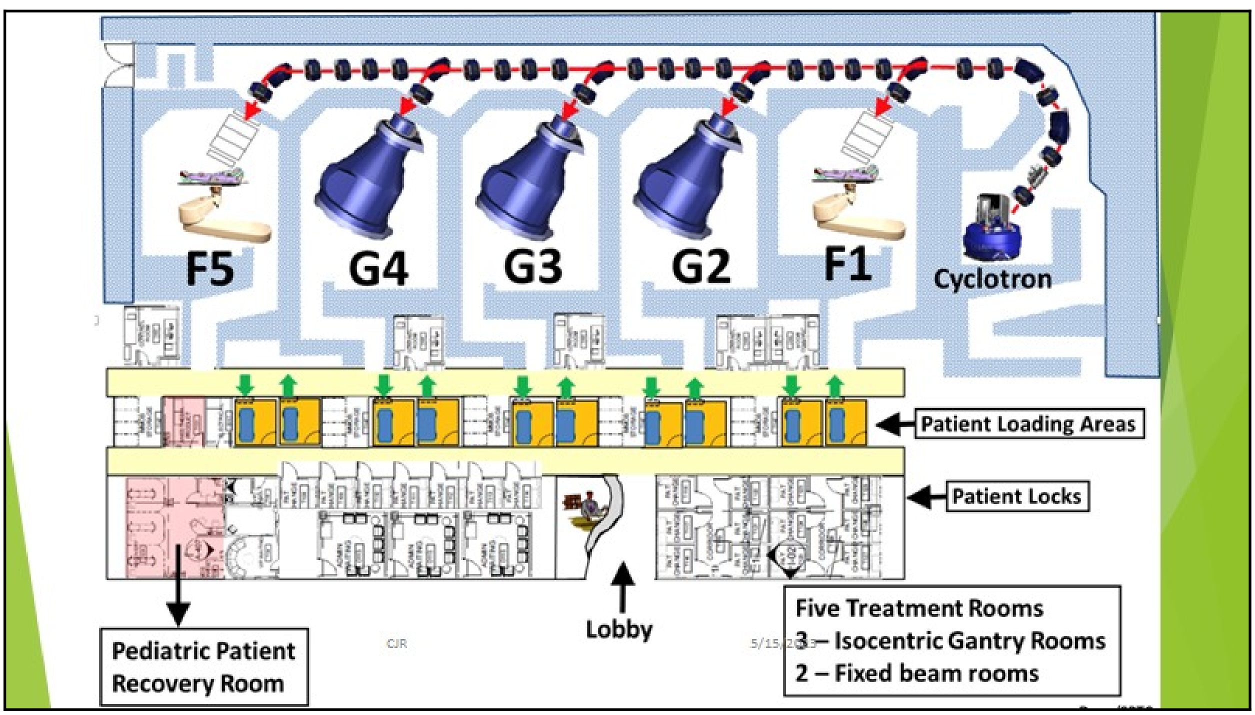
In the mid 1950s, which is the left-hand picture, people first started trying this at the Harvard cyclotron lab at the Lawrence Berkeley Lab, and needless to say they were using setups that are a little different;  just an unfocused beam coming out of the accelerator. That person on the left had a tumor in his neck they were trying to treat. Fast forward to April 1988: on the right is a picture of the groundbreaking at Loma Linda, of the world's first medical proton Center, which went into operation in 1990.



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Most centers, at least up until relatively recently, are designed like this. Here is a schematic of our facility in San Diego, where you have a cyclotron type of particle accelerator. We use a cyclotron. You can use a synchrotron. That one machine serves many rooms. The majority of rooms have an Isocentric gantry (crane that holds the beam delivery machine) so you can treat the patients from any angle. These were big, expensive units to construct with a big physical footprint among other things.


But what's happening now is that UPenn and manufacturers have developed ways to make these a lot smaller. So you have on the right a one-room version of the building I'm sitting in and it fits into a tennis court. It costs about 1/10 of what this building did, because like most things in technology, the more you build, the more companies that get into the market space, the more innovation there is. This is what's making proton therapy much more accessible, the fact that you don't need $200 million, and a big piece of land. You can put this in a much smaller footprint.

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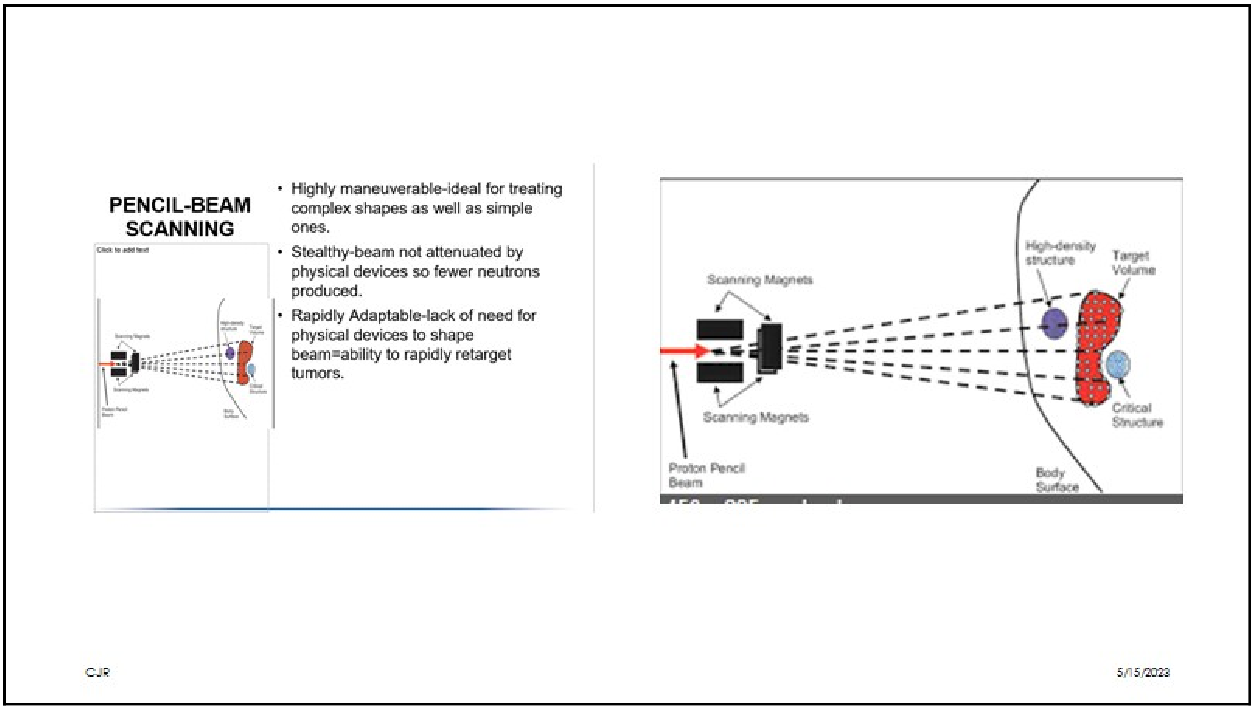


### Electromagnetic Targeting

All of the newer centers, including the one I'm sitting in, use electromagnetically scan beams to treat our targets. Rather than shaping the beam with a mechanical device, like we did at Loma Linda, we actually shape it electromagnetically, which means you can be very, very, very creative. Effectively, it's a 3D printer [pencil beam]. You're painting doses and layers, a millimeter thick, through your target. You can put high doses in some spots, lower doses in other spots. That's going to be important.

[Allen Morris note: As of three years ago, Loma Linda did not have pencil beam capability and my understanding from Dr. Rossi was that the retrofit solution is not easy and is expensive.]

A few slides down the line I will talk about intra prostatic boosting. Electromagnetic targeting allows one to change these plans quickly too. So if I have to change a plan, I can do it in 24 hours, whereas that used to be a one plus week evolution at Loma Linda to actually make new devices and all this other stuff. We can just change the data file based upon new imaging.

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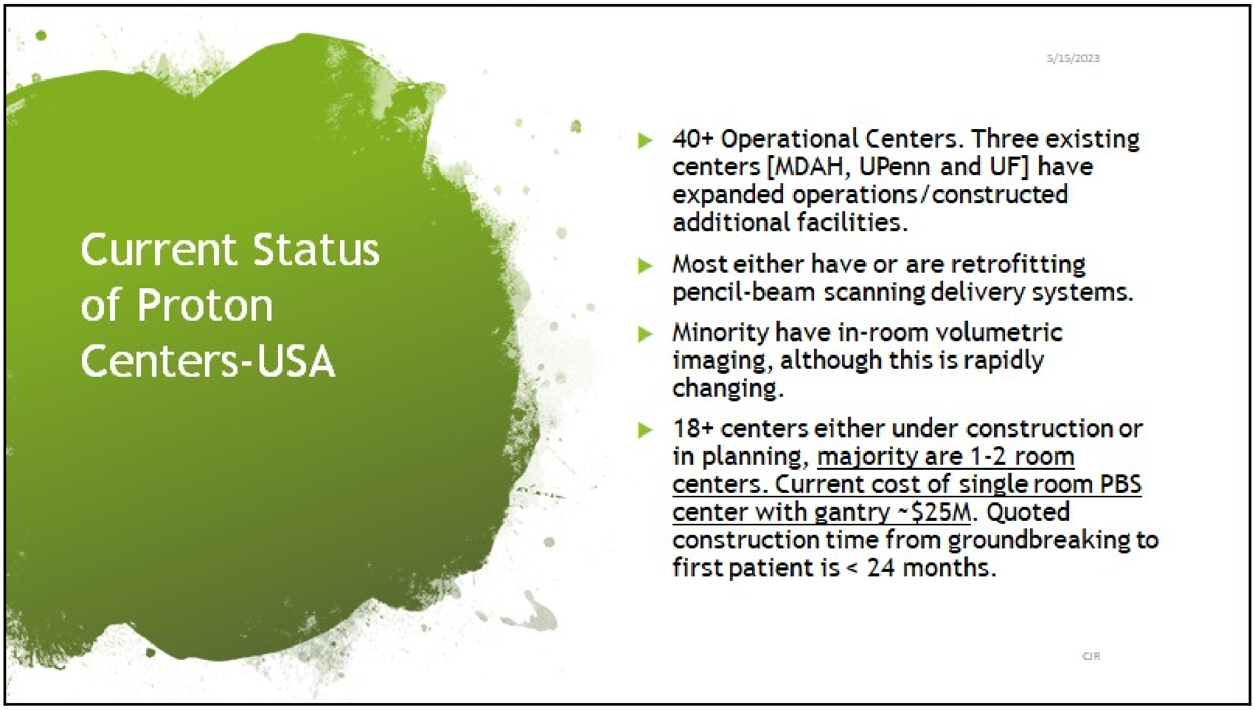


Currently, we have over 40 facilities in the USA that are operating. There are a number of existing centers that are expanding. I mentioned UPenn earlier, Mayo Clinic is expanding, University of Florida, MD Anderson, etc. Everybody that can do pencil beam scanning is doing it.

[Comment from Allen Morris: My understanding as of three years ago was that most proton centers did not have pencil beam capability. At the time, Rossi’s California Proton Center was the only one with pencil beam capability on the West Coast.]

There are about 18 facilities under construction at the moment, most are one- to two- room, smaller centers. This means the access is going to get easier. They're not evenly distributed. Of course, most of the proton facilities are located on the east coast at the big NCI-designated comprehensive cancer centers like UPenn, Sloan Kettering, Johns Hopkins, Mayo Clinic (midwest), etc. We still have somewhat of a dearth of them here out west, but that's slowly changing.

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**CT Image Guidance**

Along with this, of course, you need to be able to hit what you're aiming at. You can have all the precision in the world, but that doesn't matter if you don't have a good idea of the target. And this in prostate and other cancers goes to the importance of multimodality imaging, where you're not just doing CT scans, you're doing a CT and MRI and PET.

[Allen Morris comment: Rossi did not separate out the concept of precision real time guidance and gross planning guidance. More on that at the end].

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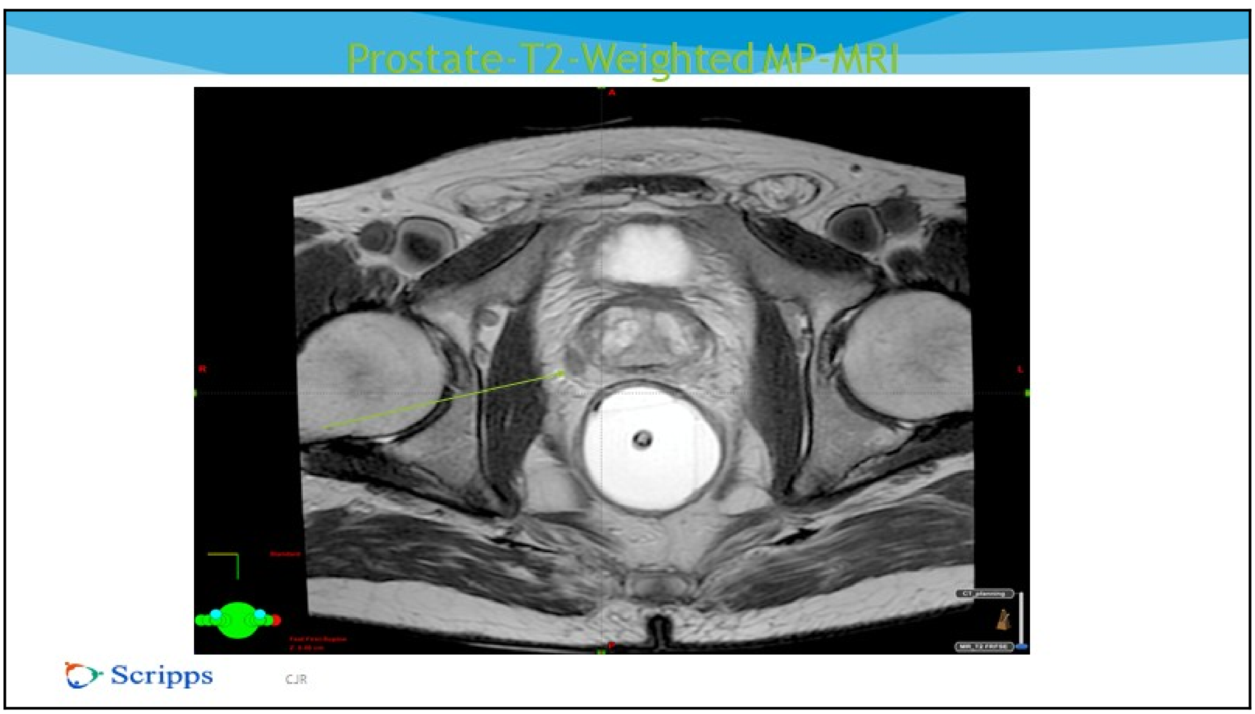
So this is your typical CT scan of the pelvis with the prostate. There in the center is the prostate and the rectum behind it and the bladder in front.  This was what most Radiation Oncologists used to do planning. ROs still use this to do planning, and it works. But where in the prostate is the cancer? If you want to hit something harder (boost), you have no idea.



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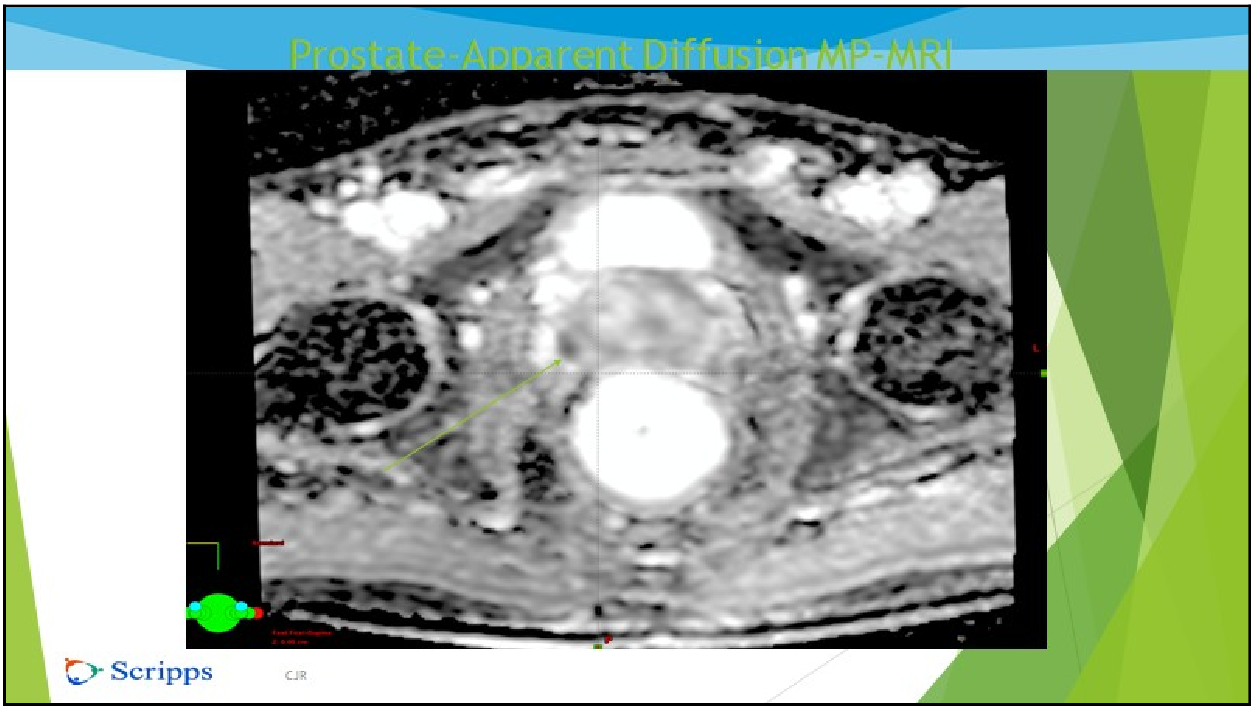
But if you have an mpMRI that you can throw on there with the same patient, you can see on the left hand side, it's actually the right hand side of the prostate left hand side of the screen that little dark circle that is the dominant tumor in the peripheral zone. So now you can target that. I got the arrow pointing at it.




And this is using different Magnetic Resonance diffusion weighting sequences (multiparametric MRI = mpMRI) to confirm that that's the focus of interest, that that’s the area you want to treat. And that means you can see it, you can tell the computer to put more dose there, and that's exactly what you do.

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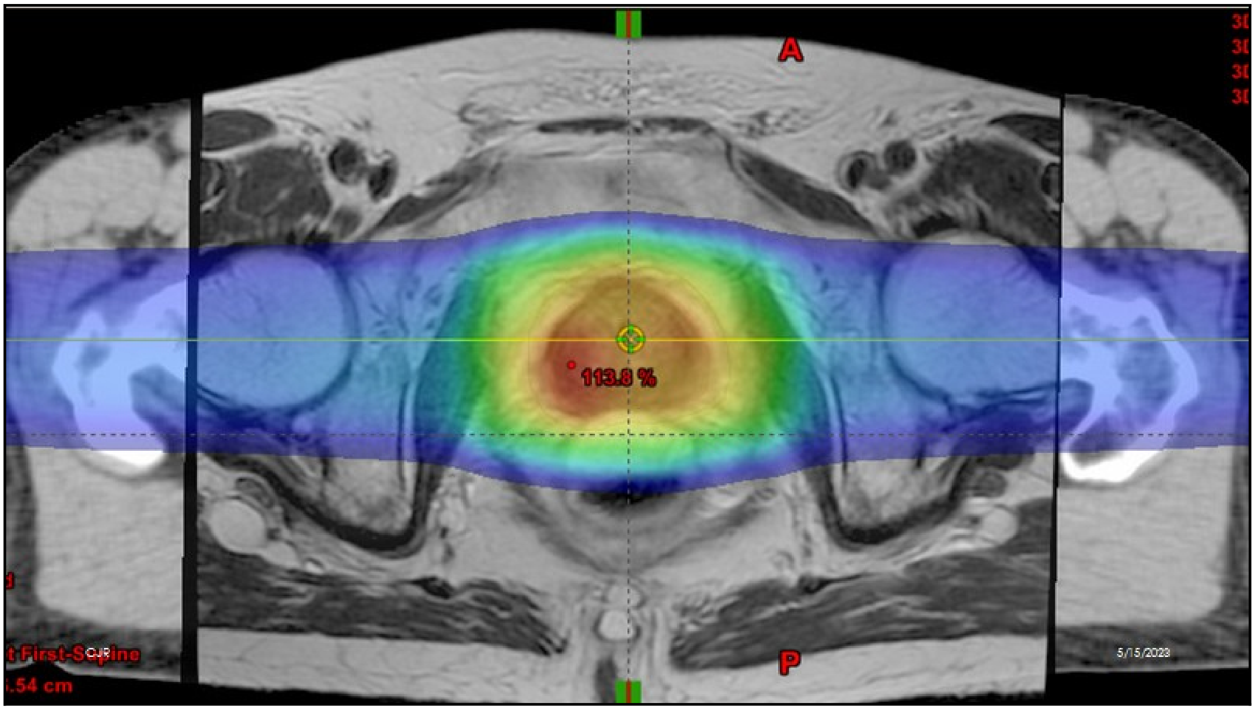
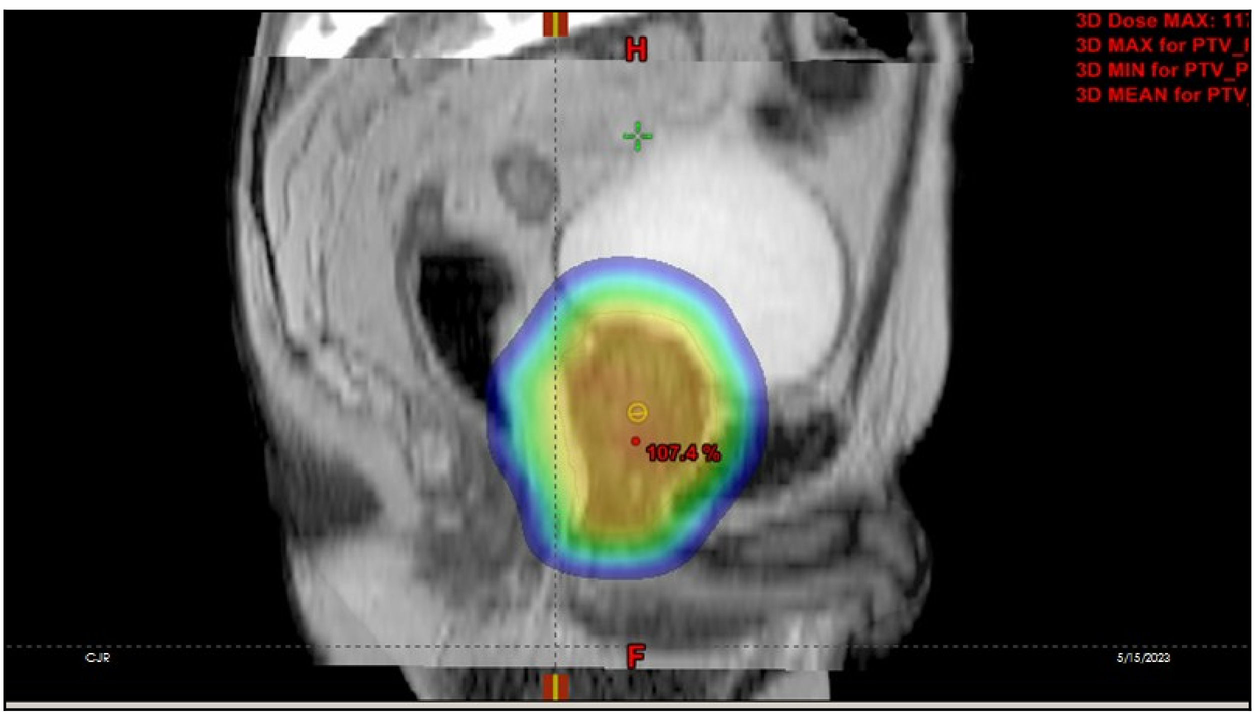
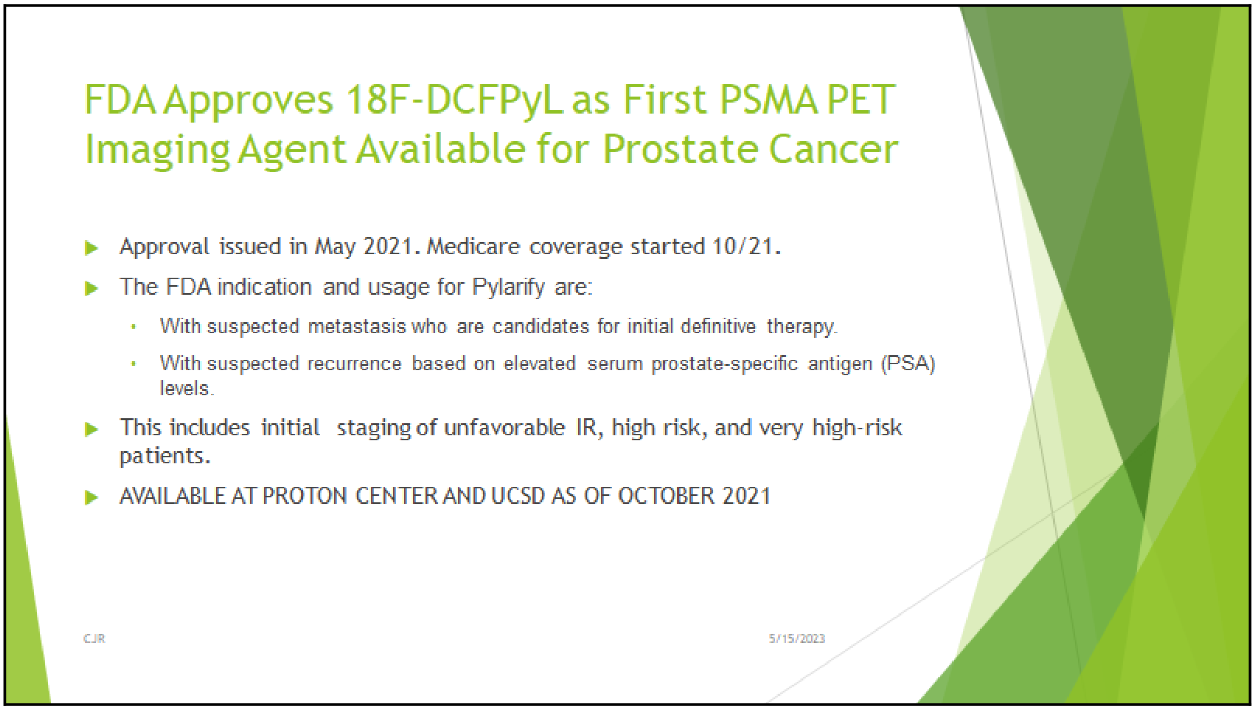



This is an example of using two proton beams to cover that area. In this case, the portion of the prostate containing cancer was getting about 15% more than the rest of the gland (a boost). We actually go to higher doses now than that.




This is looking at the same patient cut laterally and this illustrates the difference if you think back to those pictures I showed you of IMRT where you had dose from skin to skin. Here you can see the dose is concentrated in the prostate. Once you get beyond the blue edges, this blue color wash, the dose is zero. So you're not treating the intestines, you're not treating as much of the bladder, you're not treating the rectum, and you're not treating bone marrow.

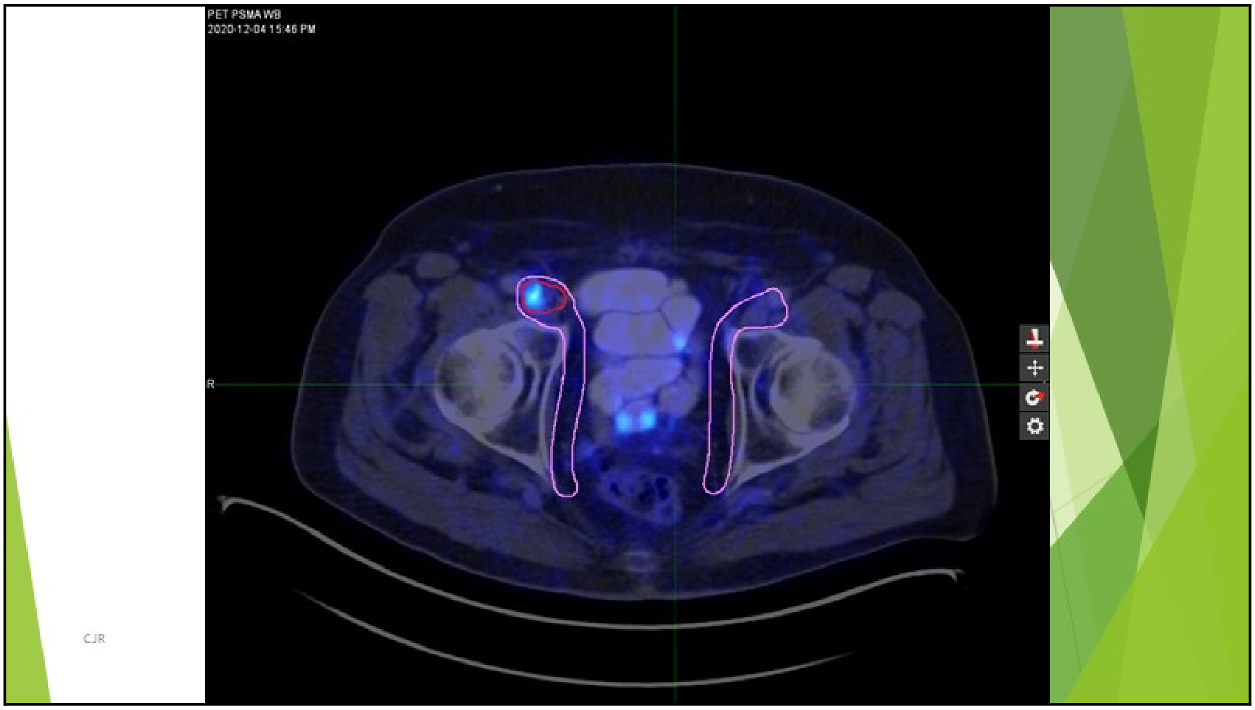



The FDA approved Pylarify F18 PSMA-PET May 30, 2021, just for diagnostic purposes. One of the things I was pleasantly surprised by was how quickly Medicare jumped on the bandwagon, in October 2021. And we've been doing these scans here as soon as we could, October 2021.

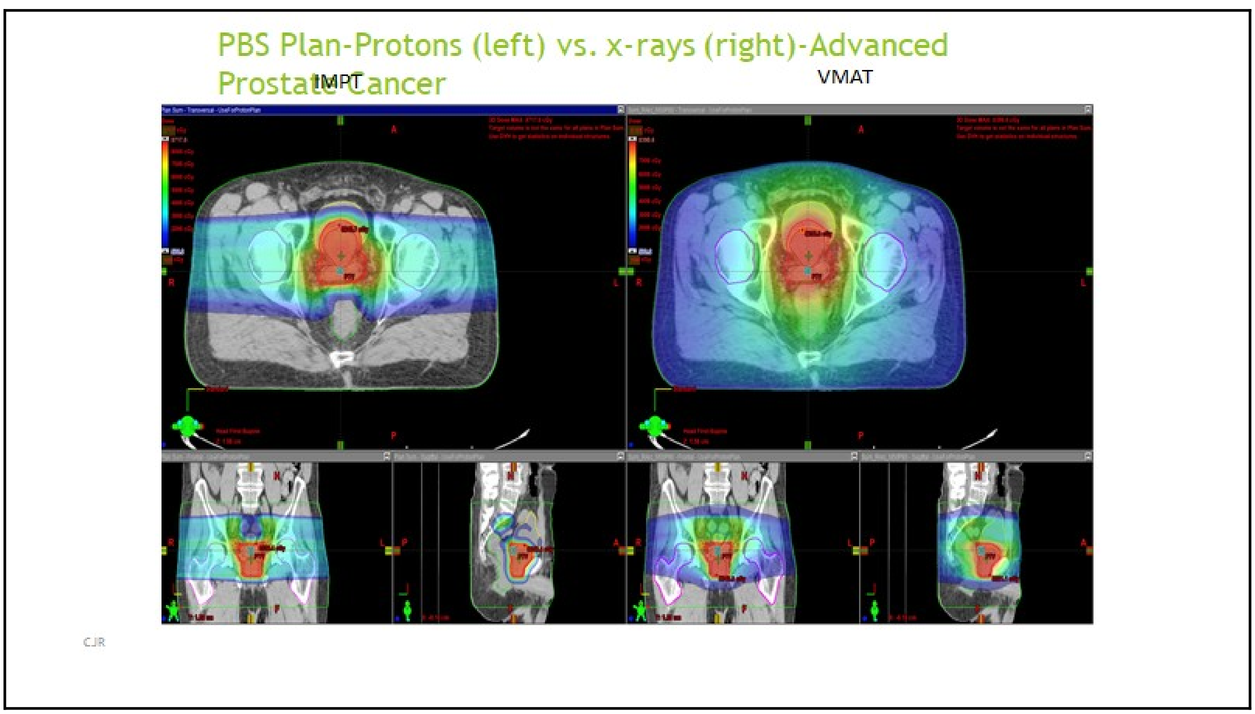
[Comment from Allen Morris: Dr. Rossi used my Stanford Pylarify study in June 2020 to design my target plan, off label. Since Dr. Rossi has been doing PSMA/PET overlays since 10/2021, he has been doing them for 1 and ¾ yrs. This modality is for target planning; not real time guidance].

And we do them more and more all the time because they're fantastic not only for workup, but also fantastic for targeting.

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**




So you're wanting to target pelvic lymph nodes, you want to boost the lymph node in an oligometastatic patient. Here you go, here's your target.. Formerly, under standard CT imaging, the lymph node in question would look normal. But with the taking up of Pyl (Radioactive Ligand, Pylarify F18), it's telling you okay, there is your target, active disease, so you want to hit that harder with a Boost.



[Allen Morris question:  One of the things I do not understood about the simulation of the off-target bath dose by Proton (as seen on the left (3) images above - specifically, the top transverse and bottom right sagittal views) is that I think it does not show an entrance bath. Or does it?
If you look at and accept the Bragg Peak graph (see earlier in the lecture), please note the non-zero entrance dose.
I suspect I just don’t understand where the beams are entering the body. The gantry went to 3 different positions for my treatment delivery x 25 days; more for my 10 days of SBRT (boost). The 3 positions seemed like 45 angle movements to me.
The question stated another way: The Bragg Peak graph has an entrance dose. Where is the entrance bath on the transverse and sagittal cuts on the left, proton simulation?]

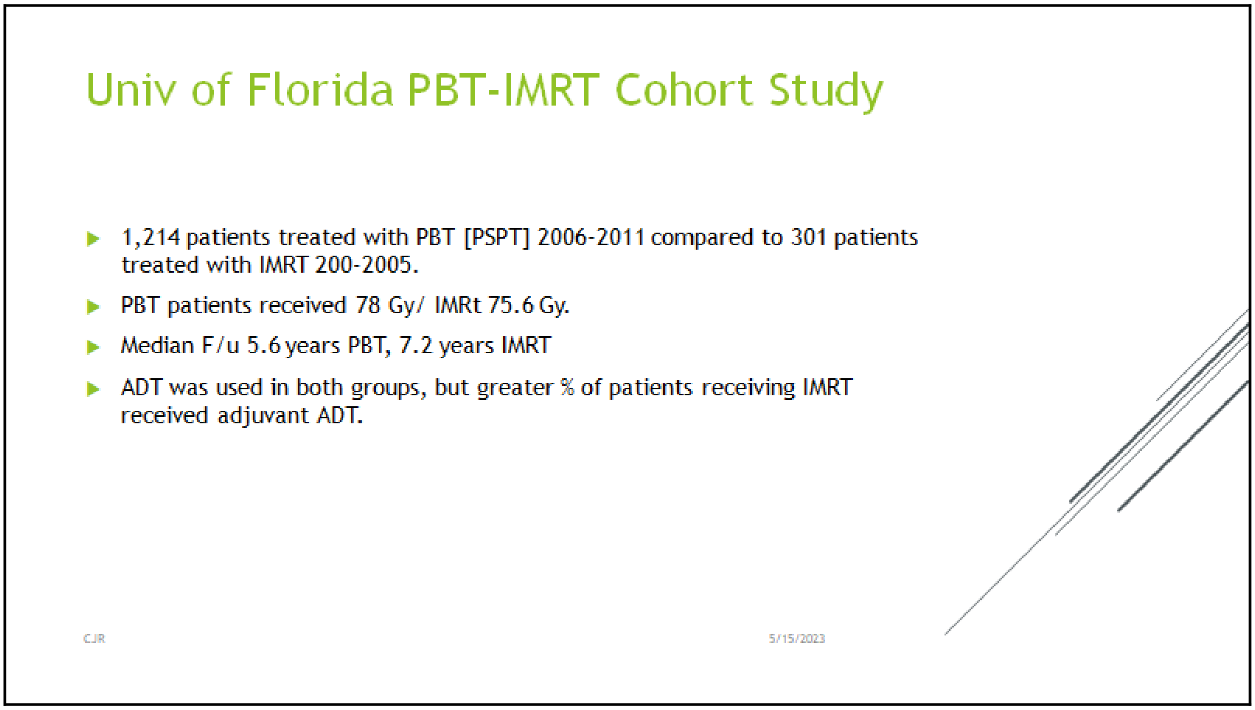
Here is a sample of a couple of treatment plans. Let’s compare a proton therapy patient to the same patient being treated with IMRT. Same target in this case for treating the prostate and pelvic lymph nodes. Dose to target is exactly the same, so no different which means the disease response (overall survival) is going to be the same. The difference is this dose bath (Off target volume).  All this tissue you see on the right now blue area, which is not being treated in the proton plan. And that's perhaps better illustrated, when you look at the midline sagittal cuts here down in the bottom, where the X-rays are going here, there and everywhere covering the whole bladder covering the vertebral bodies, etc (Off target toxicity - Organs at risk). With protons, you don't have that.


**Proton therapy vs. IMRT: head to head comparison data**

Some recently published data on treating intact prostate primary curative intent PC treatment.

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**

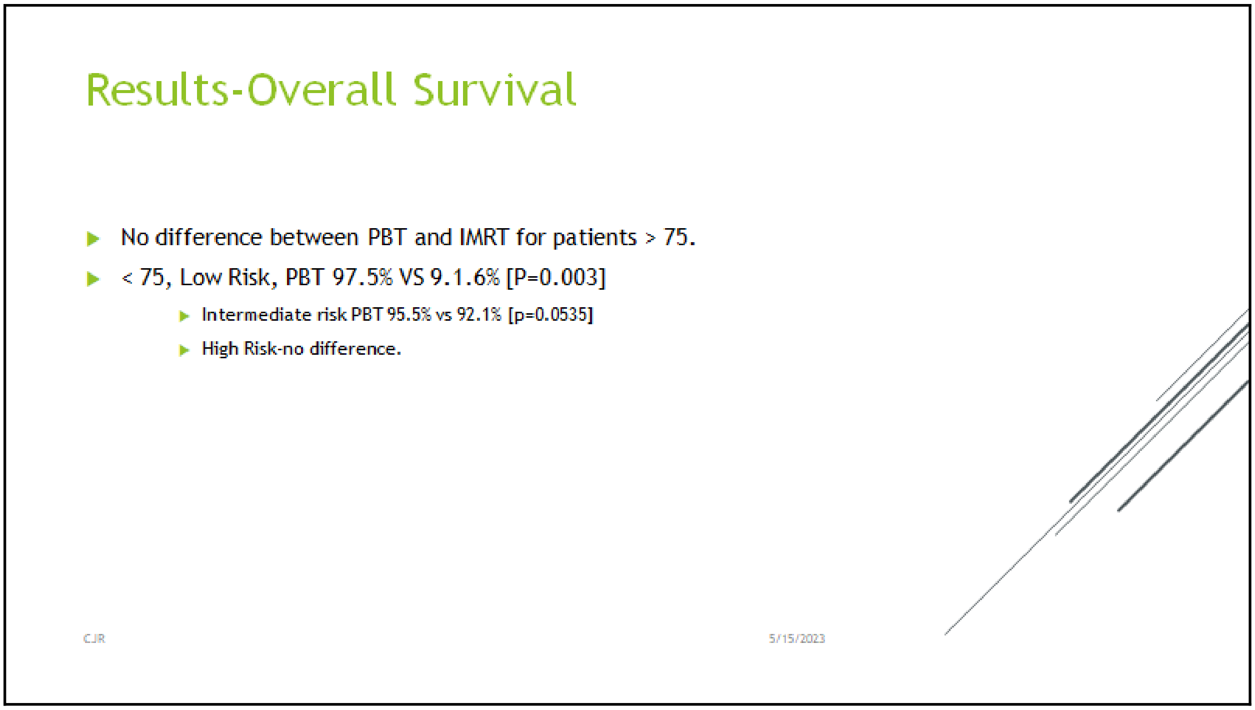
[Allen Morris comment: primary curative prostate cancer treatment is the bread and butter of proton centers - a proton centers number 1 treatment scenario by far - what keeps proton centers alive vs. proton’s best purpose: pediatric brain tumors, a rare population and thus not a significant revenue generator.
I was treated at the California Proton Center x 25 days. Most of the patient’s I talked to were prostate cancer patients. I met only one brain tumor patient. Admittedly my sample was small.]




First, we'll talk about some longer term stuff. This is going back really over a decade, if not more. The University of Florida's proton center compared their proton patients to those they treated at the same institution with IMRT. Basically the same radiation dose; actually maybe a slightly higher proton dose. They use hormonal therapy in both groups. The follow up was pretty similar.

[*Allen Morris comment: The IMRT cohort dates 2000 to 2005 vs. the proton therapy cohort dates 2006 to 2011 - Not exactly a fair comparison. Note: the study ends in 2011. This talk is a 2023 talk, which is testament to the dearth of studies in this area. Admittedly, Dr. Rossi in the Q and A with Amit mentions a randomized MSK trial published in the last month of whole craniospinal radiation in breast cancer patients, comparing proton therapy vs. IMRT and that proton was less toxic and had better disease free survival [DFS)*].

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**

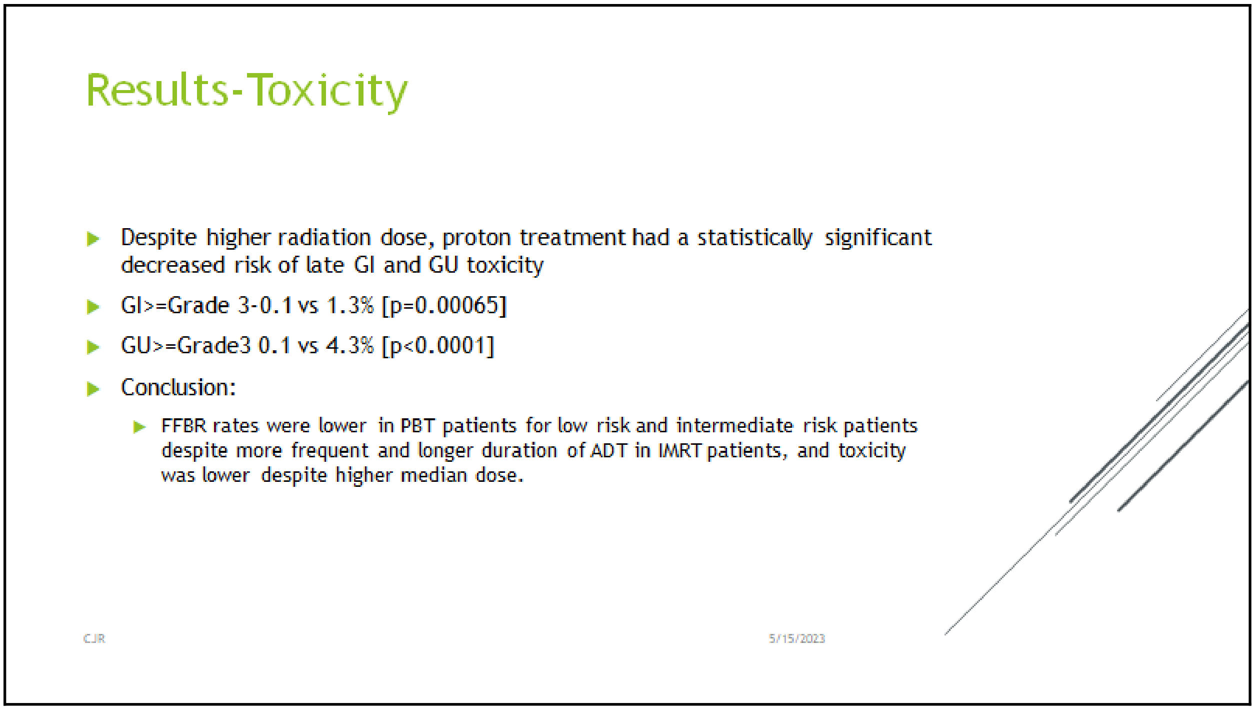



What the University of Florida found, first of all, is that they didn't see any difference in overall survival. Are you alive or not?

[*Allen Morris comment: There are only rare reports comparing head to head proton therapy vs. IMRT. In other words, there is a dearth of evidence to justify the additional expense of proton therapy over IMRT. Which is why, in part, insurance companies did not usually cover Proton, at least, not when I got proton radiotherapy from Dr. Rossi, three years ago.*
*Dr. Rossi indicates the cost is coming down significantly for many reasons including:*
*1. 1-2 gantry systems that are a fraction of the size, now costing $10 million and an ongoing competitive manufacturing market*
*2. that it is now largely a contract issue and not a medical issue*
*3. that historically radiotherapy adoption of IMRT and VMAT was based on better radiophysics and not randomized clinical trials, and the radiophysics is significantly better for Proton*
*4. That cost is a function of the number of fractions and proton therapy can in some cases be delivered in fewer fractions.*
*5. Cyclotrons last 25-30 years and Linac has to be refurbished every 3-5 years*
*Per my case: Dr. Rossi graciously gave me a generous out of pocket deal. I wanted to thank him for that, during the Q and A, but I thought that might be inappropriate.*]

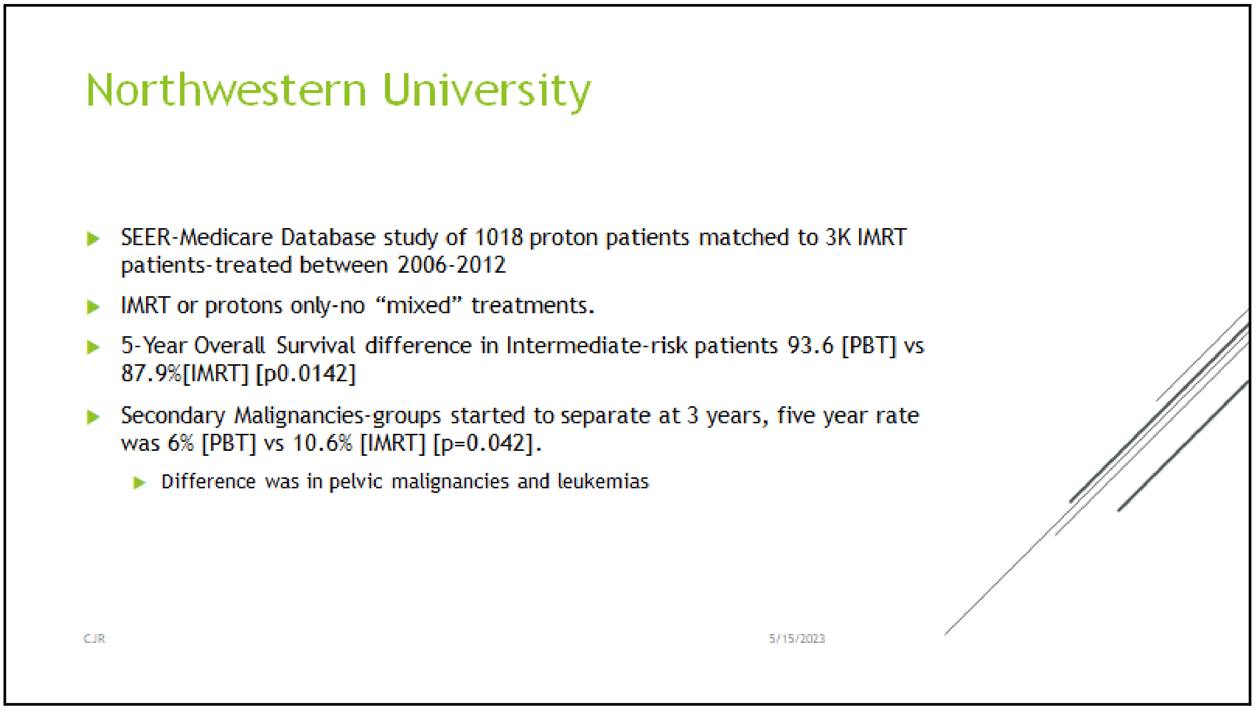
**Concerning Overall Survival**

Between proton therapy and IMRT, especially if the patients were older, there may be a small difference. It wasn't huge, but it was there in patients with low and intermediate risk disease, where there were a couple of percentage point improvement in overall survival favoring the proton patients, likely because of better local control and not having other problems related to radiotherapy.




More importantly, the University of Florida researchers saw that there was a reduction in significant toxicities, both GI which are primarily rectal injury and GU for bladder function favoring the proton patients. And that was their conclusion: that despite the fact that they were giving higher doses in the proton patients, they were seeing that they had a lower toxicity rate, and that they had higher freedom from biochemical recurrence. And they were able to do this without having to use hormonal therapy for as long a timespan [ADT free survival] was certainly good.

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**

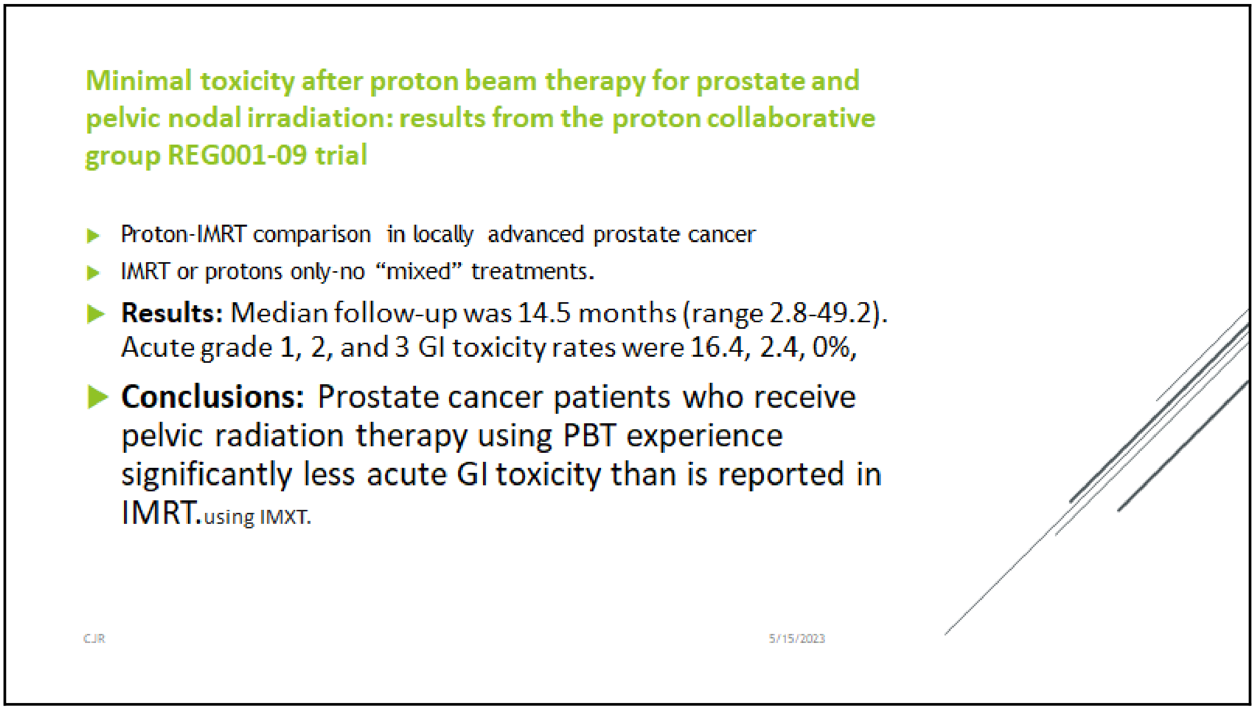



The folks at Northwestern, also a proton Center, did a big Medicare A database mining thing, which you all kind of have mixed feelings about some times.
[Allen Morris translation: This is a retrospective population study with all its inherent flaws].
They were comparing IMRT prostate cancer patients and proton prostate cancer patients and they saw that, again, there was a difference in overall survival, favoring the proton patients.

This difference was primarily because of the increased incidence of secondary cancers in the X-ray therapy patients, which you're going to hear more about in just a few slides. The difference, when you looked at why IMRT patients were more likely to pass away, is that they were more likely to develop either a solid tumor in the pelvis [Rosalind Franklin] or leukemia, [Marie Curie] because you're splashing that X-ray dose here, there and everywhere. You're treating more normal tissue, and therefore you're more likely to induce a radiation-created cancer.

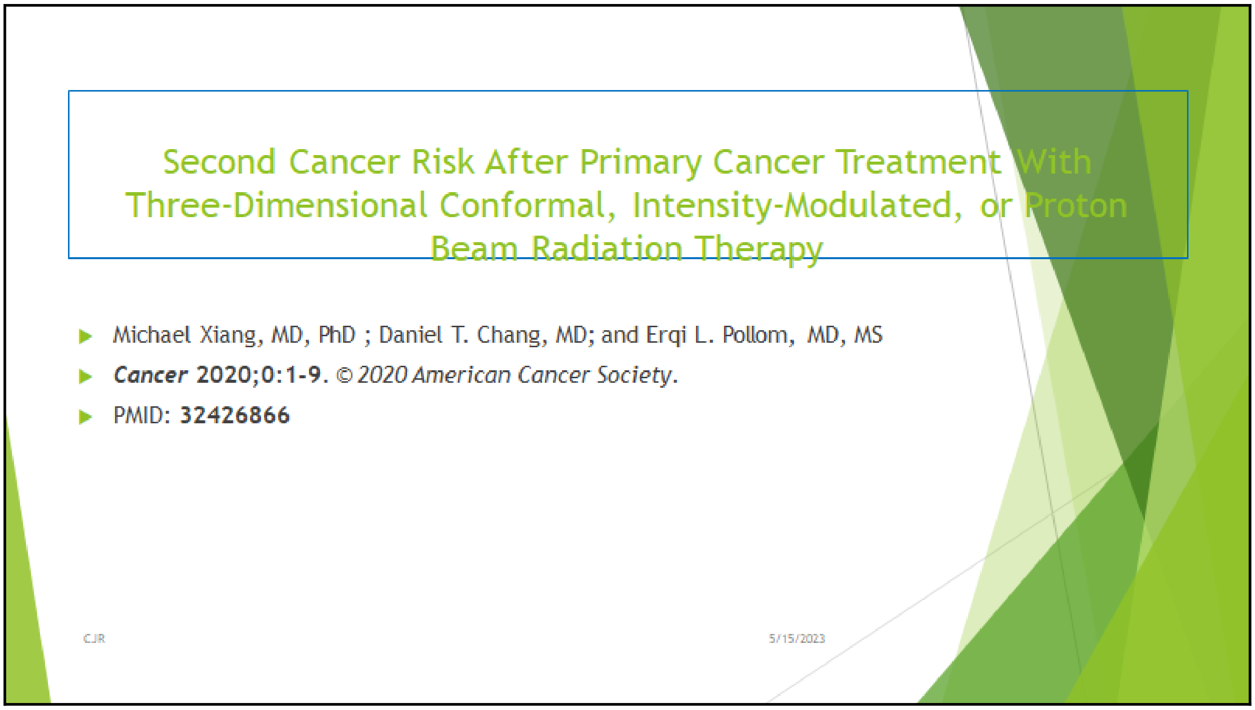
[Allen Morris comment: The 5 year rate of secondary cancers: copied from the above Northwestern slide was 6% for Proton and 10.6% for IMRT. – Is this a typo? If this is not a typo, that is an unbelievably high, concerning rate; but admittedly a significant 4.6% advantage to Proton therapy.
Secondary cancers, a late toxic side effect of RT, probably are not very important in short lived cancers such as pancreatic cancer; but would especially impact long lived cancer patients. And if the above figures are correct, way more underrated than I thought.
The prototype of long lived cancer patients are prostate cancer patients; estimated prevalence 3 million in the USA; the highest prevalence of any cancer by far except for breast cancer, also estimated at 3 million survivors.]

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**



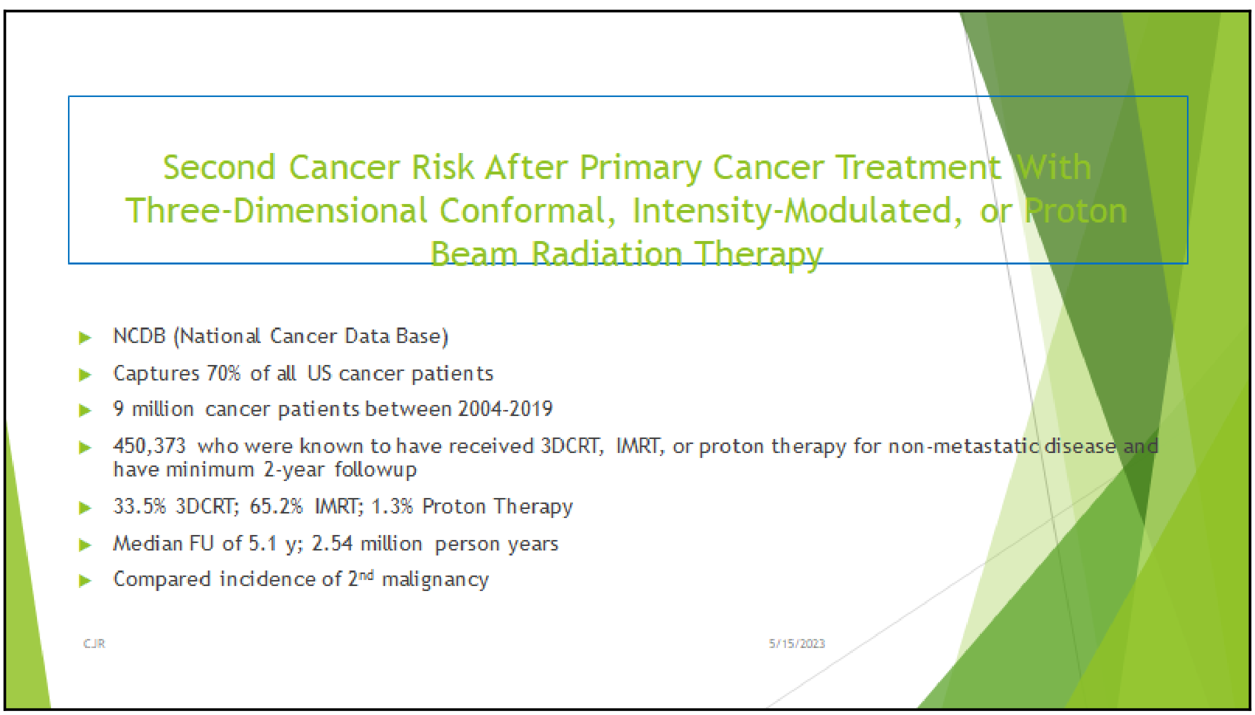

Another publication came out of a big registry study. I am one of the authors on this one where we were looking at the same kind of comparison. And what we found is that if you have to treat the pelvis in prostate cancer and you do that in some more advanced cases, we created a lot less toxicity using protons to treat the pelvis than IMRT because you weren't treating the intestine because protons we’re not exiting through the intestine. This is not to say IMRT is bad. It's a really good treatment. But it just shows that once again, if you don't treat a tissue, if I don't hit the intestine, I'm not going to hurt it. I'm not going to affect it.

## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]



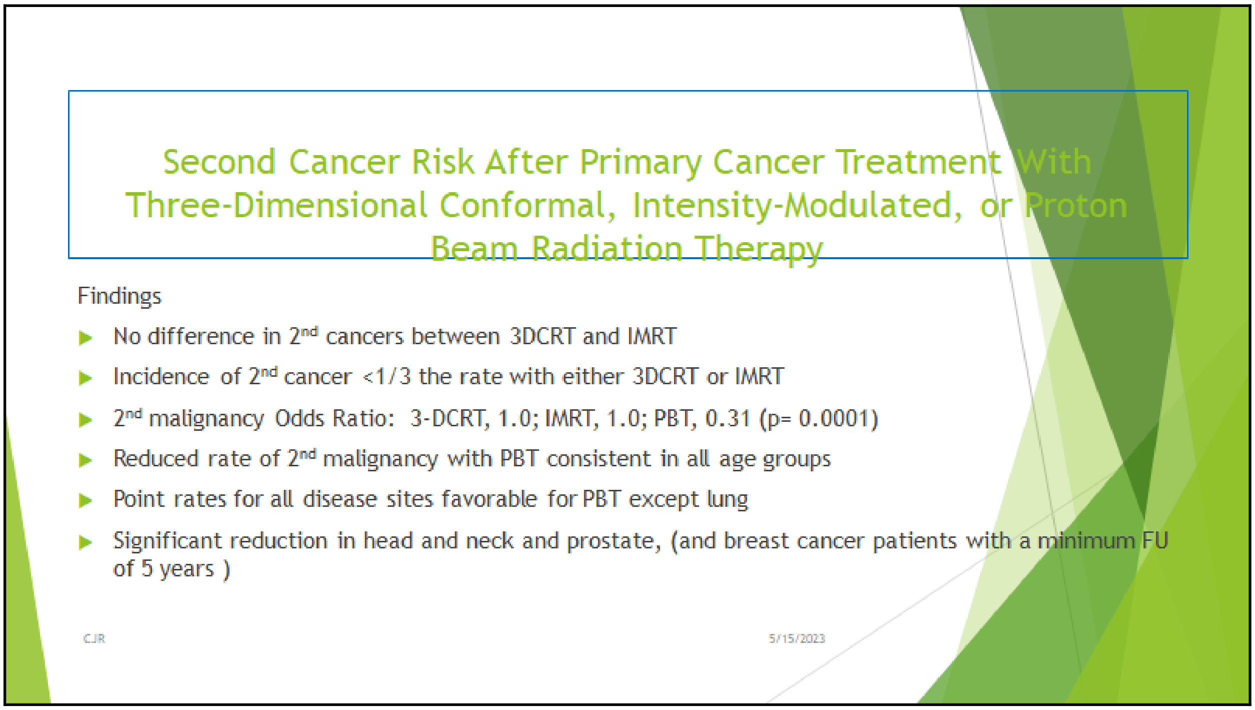

**Secondary Cancers**

Second cancers - I'm going to talk more about this. This was a very interesting paper that came out about three years ago, published in Cancer. The authors were looking at patients who had the 10 most common adult cancers, not just prostate cancer, where they were treated with 3d conformal X-ray therapy, which was the standard in the 90s and early 2000s; or IMRT, which is the standard today; or protons. Did they see a difference?



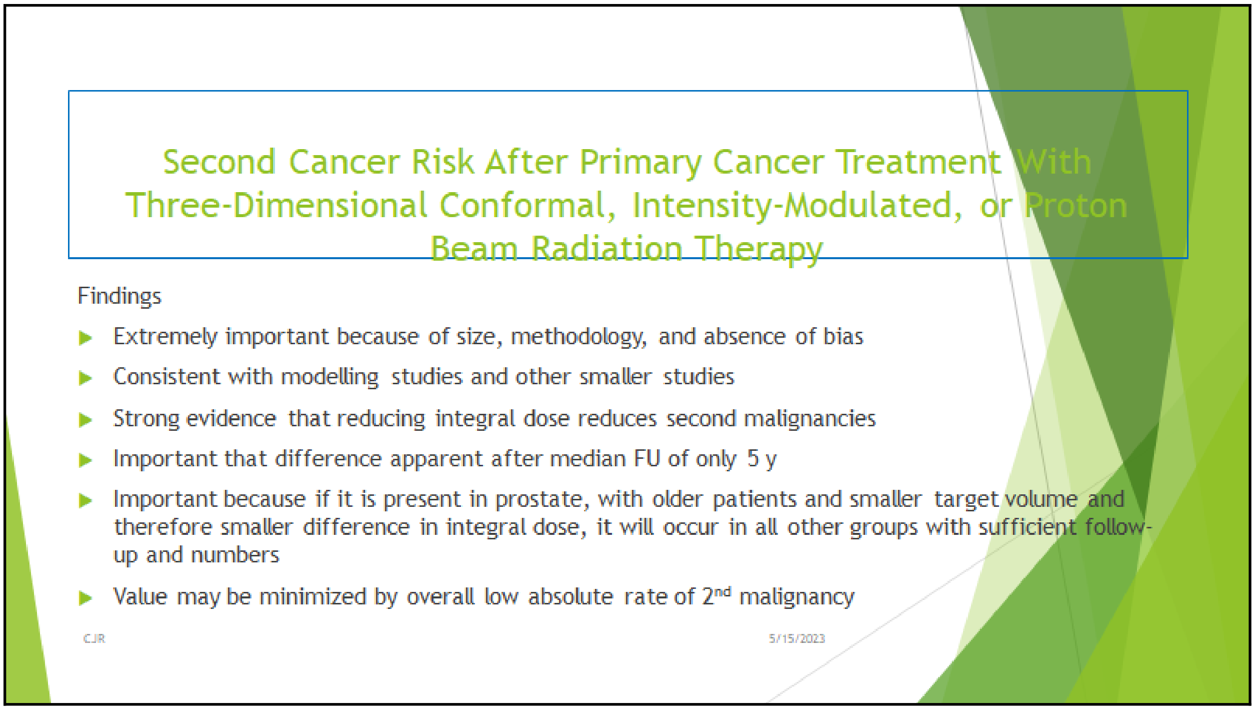
## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]

They looked at 70% of all the cancer patients in the country using this database, thus lots and lots of patients to review, a good sized data set. There are always problems with the bigger views (population studies). But still, you're looking at lots and lots of patients that you can probably draw some pretty good, at least broad brush conclusions.




They found that, first of all, when they compared the different types of X-ray therapy, they didn't see a difference in second cancer rate, which surprised a lot of us because if anything with IMRT, you would expect it to be a little bit higher, because you're bathing all that tissue to a greater extent than 3d conformal. But what they did find is that the proton patients had second cancers incidence less than 1/3 the rate [emphasis] that was seen with either type of X-ray therapy. They saw that in nine of the 10, adult malignancies. They didn't see it in the lung cancer patients, probably because lung cancer survival was pretty short [in stark contrast to prostate cancer patients who are the prototype of long lived cancer patients]. But it was consistent across all the age groups. And it was significant for all these different cancer sites except for lung cancer. Not a surprise, we have mathematical models that are used for radiation protection, the ones that are better used are part of ALARA. Mathematical models, of course, need to be verified with real human data. If you think back to the pandemic, we had lots of really scary mathematical models that thankfully, didn't come true.

[AM editorial: Scariness did come true: over 1 million people died in the US due to Sars-Cov2; overnight the 2nd leading cause of death; only mitigation measures including the vaccines prevented Sars-Cov2 from being even scarier. I suspect the even scarier >2 million death projections are what Rossi is referring to. A corollary of the success of mitigation was the virtual absence of the Flu and RSV for the 2020-2021 season, lowest incidence recorded ever despite markedly increased testing/surveillance. https://www.cdc.gov/flu/season/faq-flu-season-2020-2021.htm].




The reason the Stanford study was so important included not only primarily the size and methodology, but also because it wasn't done by people who work in the proton world: it was done out of Stanford.

[AM editorial: One of the reasons the Stanford study is important to Rossi is that the larger Radiation Oncology community is not convinced of any Proton advantage over their tool IMRT and Stanford does not have a Proton machine: their advanced system is Cyberknife; so they would not have a bias toward Proton and thus would appear to be an independent arbiter. Therefore, the Stanford study casts an important independent vote for Proton therapy over X-ray.

Think about it. No Radiation Oncologist is going to say to their prospective IMRT patient, you really should consider proton therapy because it is better than what I am offering you. Am I wrong?

Case in point: My own Radiation Oncology experience -

I was in the UCLA trial that resulted in FDA approval for Gallium-PSMA, in the Stanford trial that resulted in FDA approval for Pylarify-F18, consulted UCSF radiation oncology as my closest center willing to do MetastasisDirectedTherapy, and I asked all of them about Proton Therapy. Proton Therapy is a very seductive theoretical notion due to its radiophysics advantage, the Bragg effect, yet none of them thought it had a clinical/practical advantage over IMRT Stereotactic Rx. Admittedly, that was 3 years ago. And though adoption rates now are lightning fast compared to last century when I started in practice when they were up to 20 years; they are still roughly no better than 3 years now. Therefore, I suspect, admittedly for many more reasons: Dr. Kishan (UCLA), Dr. Buyyounouski (Stanford), Dr. Hong(UCSF), and my colleague and friend, Dr. Matthew ALLEN (Redding, Valor Radiation Oncology) who was trained at Harvard and MD Anderson where there is both IMRT and Proton; all of them probably still hold the opinion that IMRT is just as good. Don’t ask me, call them up and ask yourself.]

Again, it was consistent with this other modeling data. Since surprise, surprise, reducing normal tissue dose can help.

So it had a lot of things going for it. It really does support the idea of not treating healthy tissue, if you don't have to do it. Now the overall absolute rate of second cancers is low. Again, it doesn't mean that everybody treated with X-rays gets a second cancer, it's around one or 2% in adults.

> [Allen Morris’s comments here, with apologies, are very long - the following 2.5 pages. Please feel free to skip his bracketed and indented comments which follow.]
>
> [A 2% second cancer rate, if it relates to overall survival, can be the difference in proving efficacy for a cancer treatment. So I believe, this apparent proton advantage is a big deal; especially for the few cancer types wherein a patient is more likely to “die with the cancer”, prototype prostate cancer, than dying from the cancer. And the “dying with the cancer” may be due to dying with a 2nd cancer such as CLL, myeloma, myelodysplasia/acute leukemia, lymphoma, colon ca, bladder ca, melanoma, sarcoma, among others. Do you think when the death certificate assigns death to bladder cancer that a secondary cancer is picked up automatically in some population database? “Welcome to the real world,” says Rodney Dangerfield in Back to School. The capturing of second cancer data is imperfect. Even Dr. Rossi in the Q and A session at 45:40 admitted that physicians notoriously underreport toxicity/adverse effects; and may I add especially if you are dead. The signing of the death certificate is probably the least favorite duty of a physician, especially at a VA. You should realize the Stanford study was largely a VA database; great for looking at trends not for absolute values.]
>
> [The two studies, Northwestern and Stanford, that Rossi cites attest to the difficulty at getting at the true incidence of iatrogenic (secondary) cancers. At first glance, the two studies report vastly different numbers for 2nd cancer risk.
>
> Northwestern: IMRT 10.6% vs. Proton 4%
> Stanford: “1-2% XRT with ⅓ the rate for PT” Rossi’s translation
>
> More important to Rossi, both studies are concordant on the relatively significant lower risk of proton therapy vs. RT at about ⅓ the risk. 4% is roughly ⅓ of 10.6%
> So, again the Stanford study is an important study for **relative risk advantage** of Proton over RT. This is Rossi’s point and well presented.
>
> But patients should also be concerned with what is the **absolute** risk of 2nd cancer from toxic (dsDNA breaks) RT. Which of the above, discordant absolute risk % numbers do you believe?

## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]

Me: I believe the truth is much closer to the Northwestern study if one follows patients for 10-15 years post treatment; in large part informed by

a. the two below review radiology articles and
b. in part from my own anecdotal experience as a pathologist

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2020.00989/full
Admittedly, the research is handcuffed by and I quote from the above article:
“However, prospective trials confirming this are lacking due to the need for an extremely long-term follow-up and the ethical complexities of randomizing patients between these two [Proton and IMRT] modalities. Although the risk for development of SM [secondary malignancy] is small, it is statistically significant, particularly for long-term survivors of treatment. One study conducted with extended follow-up, published by Sethi et al., reported statistically significant reductions in secondary malignancy risk in pediatric patients treated for retinoblastoma (0 vs. 14%, $p = 0.015$)

Review articles on 2nd cancers after RT:

One review article lists 2nd cancer risk after any DNA toxic therapy including chemotherapy and radiotherapy at 17-19% after an average latency of 10 years. And for prostate cancer in particular the article states “RT for prostate cancer significantly increased the risk of second malignancies by approximately 6% (95% CI, 1%–11%) as compared to surgery (p = 0.02). Increased relative risk was 15% and 34% for those who survived ≥5 years and ≥10 years, respectively.
https://doi.org/10.3857%2Froj.2018.00290

Not much of an issue at all if one is considering pancreatic, esophageal, lung, brain, or any of the short lived cancers; but for prostate cancer, the prototype of a long lived cancer; it is a concern.

And I quote from another review article:
“when data for cancer survivors are compared with those of the general population, there is a 14% higher rate of cancer among survivors”
Typically, RT-induced malignancies (RTIMs) are biologically aggressive cancers with a variable period of 5–10 years for hematologic malignancies and 10–60 years for solid tumors between RT and the development of the second cancer.
https://doi.org/10.1148/rg.2021200171

The Stanford study: Do we believe the absolute 2nd cancer risk %?

So, let’s take more than a superficial glance at the more optimistic Stanford absolute numbers.
https://doi.org/10.1001/jamanetworkopen.2022.23025

The overall prostate cancer RT cohort had a 3.7% absolute 2nd cancer rate; but with only a median followup of 9 years. So, one weakness was that the median followup just starts to capture the usual latency (late appearance) of 2nd cancers.

Next, let’s look at the cohorts and I quote:
The median (IQR) age was similar between the cohorts (66 [61-71] years in the radiotherapy cohort vs 65 [60-72] years in the nonradiotherapy cohort). Patients in the radiotherapy cohort vs the nonradiotherapy cohort had higher Gleason scores (eg, Gleason score >8 points: 8601 patients [16.3%] vs 8944 patients [9.8%]; *P* < .001) and higher clinical tumor stages (eg, stages T2 and T3: 17 089 patients [32.3%] vs 25 837 patients [28.4%]; *P* < .001). A greater proportion of patients in the radiotherapy cohort were Black or African American (14 754 patients [27.9%]) compared with the nonradiotherapy cohort (23 042 patients [25.3%]; *P* < .001).
In summary, the RT cohort had higher Gleason scores, higher tumor stage, more blacks, and 1 year greater age. All risk factors for shorter overall survival.
AM translation: The radiotherapy group had a much greater likelihood of dying just with prostate cancer and never having the longevity to develop a 2nd cancer which explains in part why the absolute Stanford numbers are less than the Northwestern numbers.

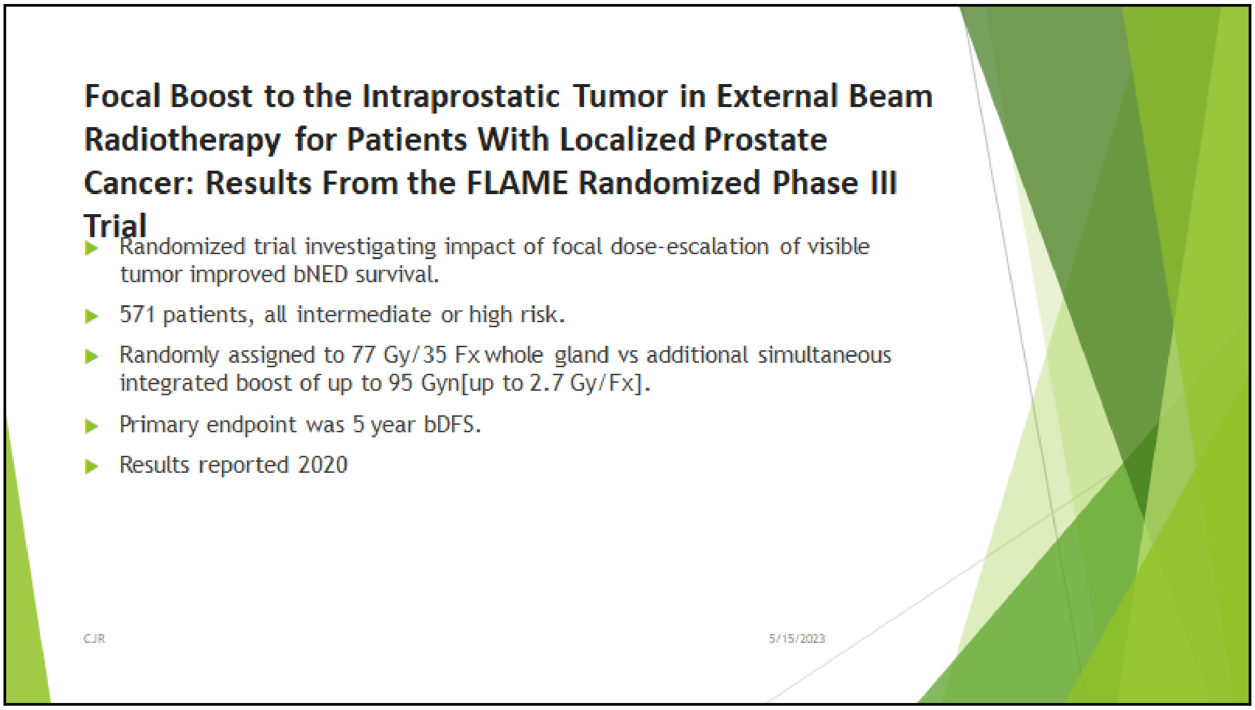
[AM anecdotes: AM has seen several breast cancer patients, in his career as a pathologist, who have had lumpectomy and radiation RT for a low risk, probably non-life threatening breast cancer, who are non-smokers, who have developed a fatal lung cancer in the same, ipsilateral lung (radiation field) as their breast cancer; including a local radiologist’s wife, a tragic story.
I know that none of my above anecdotal patients were captured as having secondary cancers in a database; not even the 70% nationwide huge (Stanford study) database. Yet these patient’s breast cancers were captured in our required cancer registry; required for cancer center designation].

In summary, what was important to Rossi was that it was a fair comparison between RT groups. And Proton had ⅓ the rate of cancers as x-rays (IMRT).]

But we use lots of radiotherapy and treat lots of people. So those small numbers do become important when you apply them to several 100,000 people, your United States.

What else do we have recently?

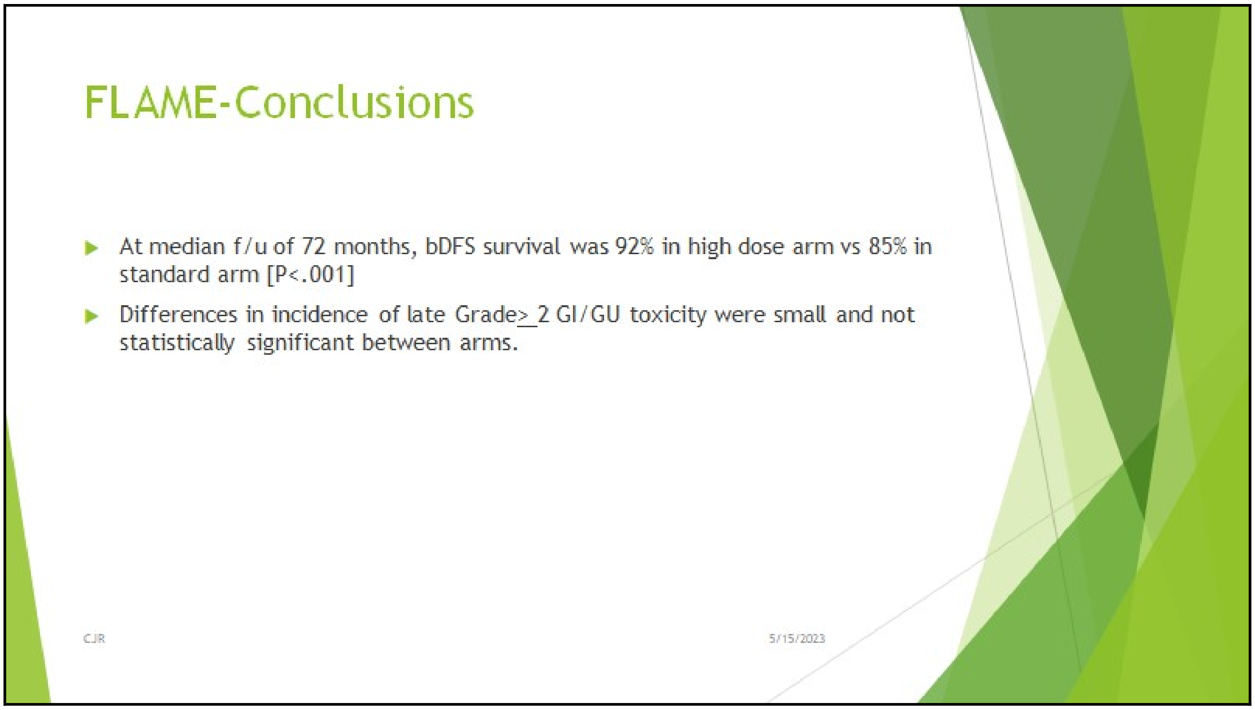
## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]



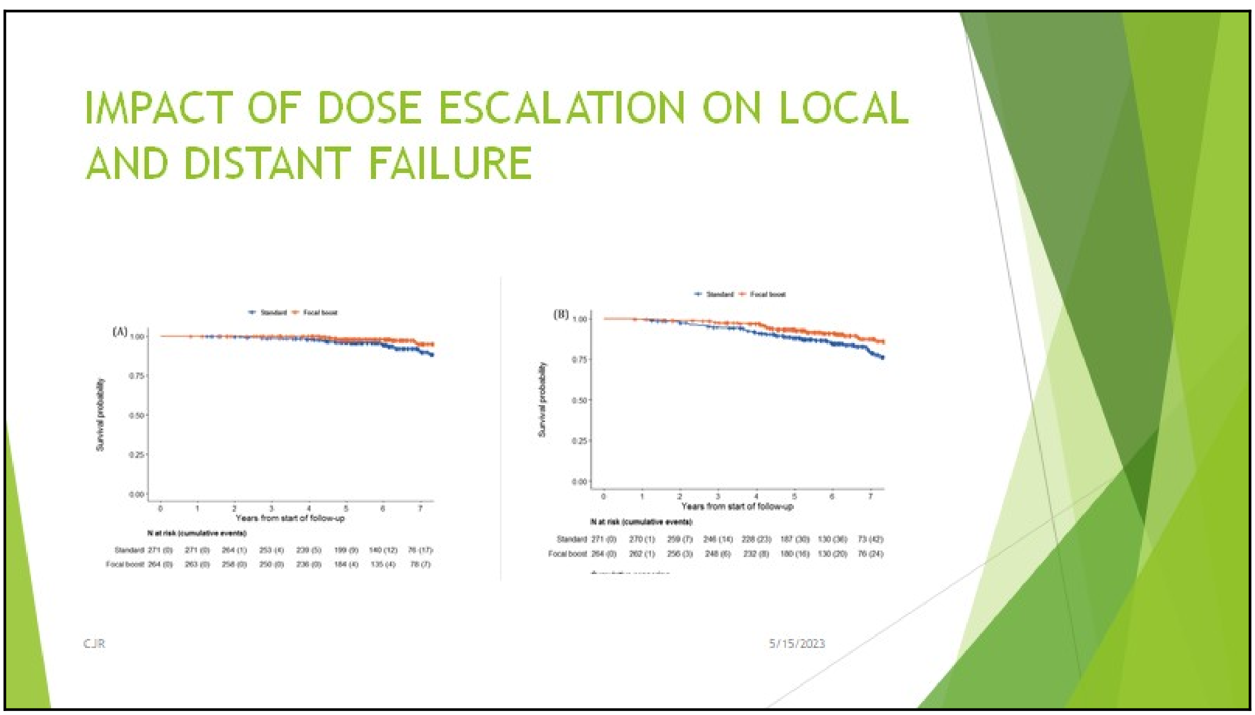

**Intraprostatic Boost Therapy to the Tumor**

There's a lot of interest in this idea of doing intraprostatic boosting. Let's hit the cancer in the prostate higher, put a higher dose in that area that is malignant. There's this trial called the FLAME trial where they were actually looking at this in a randomized fashion. So half the patients got 77 Gray, a pretty good dose to the entire prostate, and the other half got the same dose to the entire prostate, but then had a boost that was given simultaneously, where they were giving up the 95 Gray to whatever tumor they could identify.

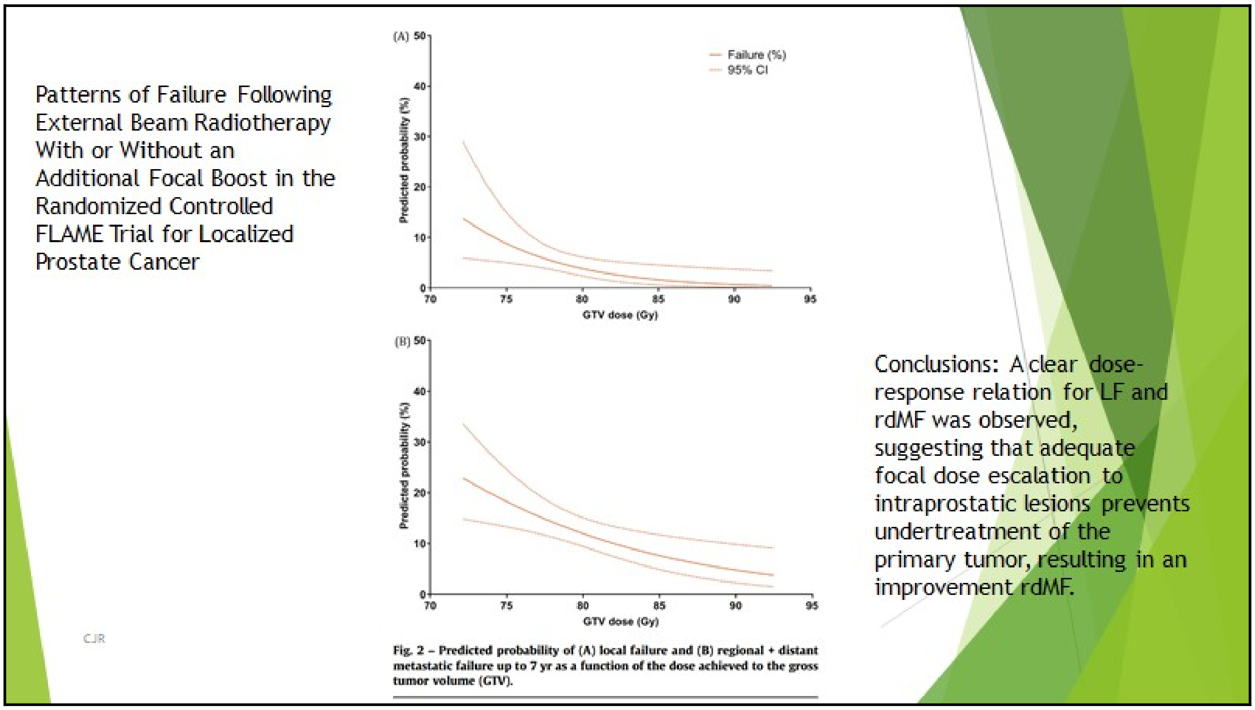
## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]




These results were reported in 2020. They found that the disease free survival, DFS, was about 7% higher in those patients who got the boost within the prostate versus those who didn't. **T**hey did see a slight difference in toxicity between the groups. But it was small, and it was not statistically significant. So it really supports the idea of doing what we all do now. And that is if you can identify a target, which means your imaging is showing you something, you want to hit it harder.

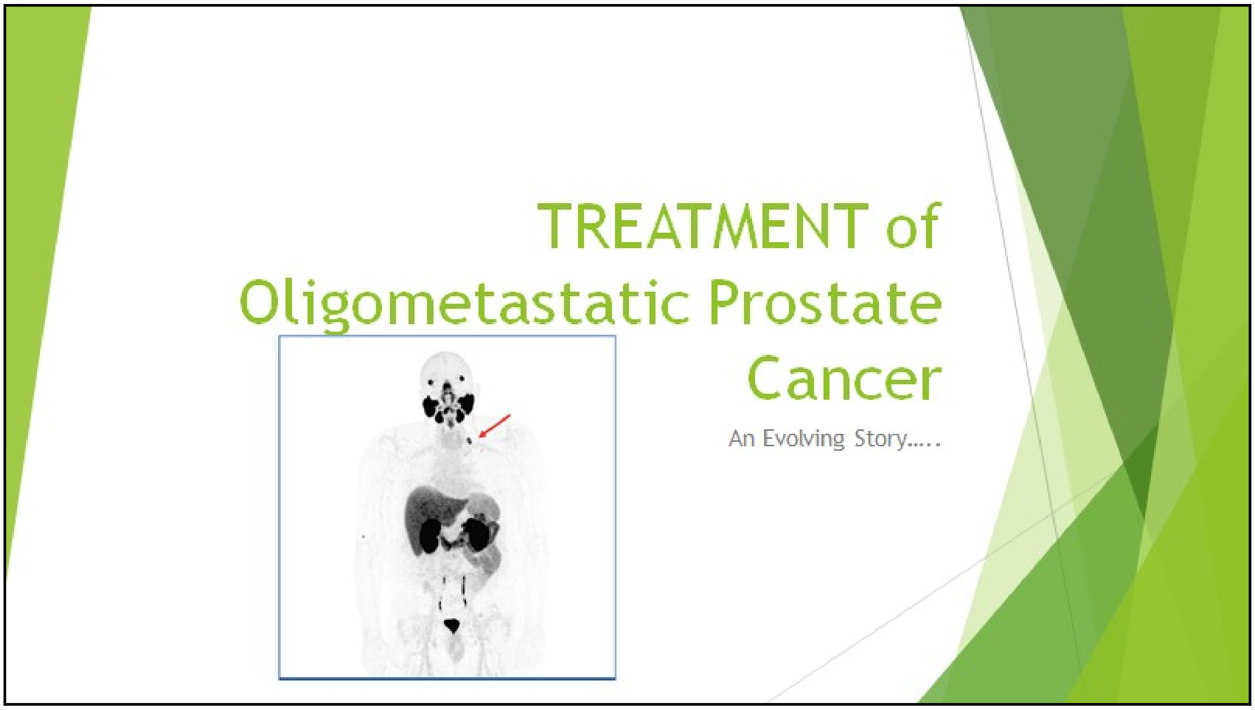


And this is just giving you an idea, again, these curves separate, they found that this curve on the left is looking at the impact of a dose on survival, showing that the focal boost of the red line patients had a higher survival over time. And also they found, not surprisingly, that if you control the disease locally, you get a decreased risk of distant failure. And that's what they're seeing here. If you have locally uncontrolled cancer, it is more likely to throw off metastasis. When we try to control local disease to the best extent we can, then more of the same thing.




They were looking at patterns of failure. And sure enough, they saw a clear dose response relationship, the higher the dose you could give, the lower the probability of either local failure or distant failure. This doesn't come as a surprise. This is what all of our radiobiology predicts. But it's been good to verify this in human beings.

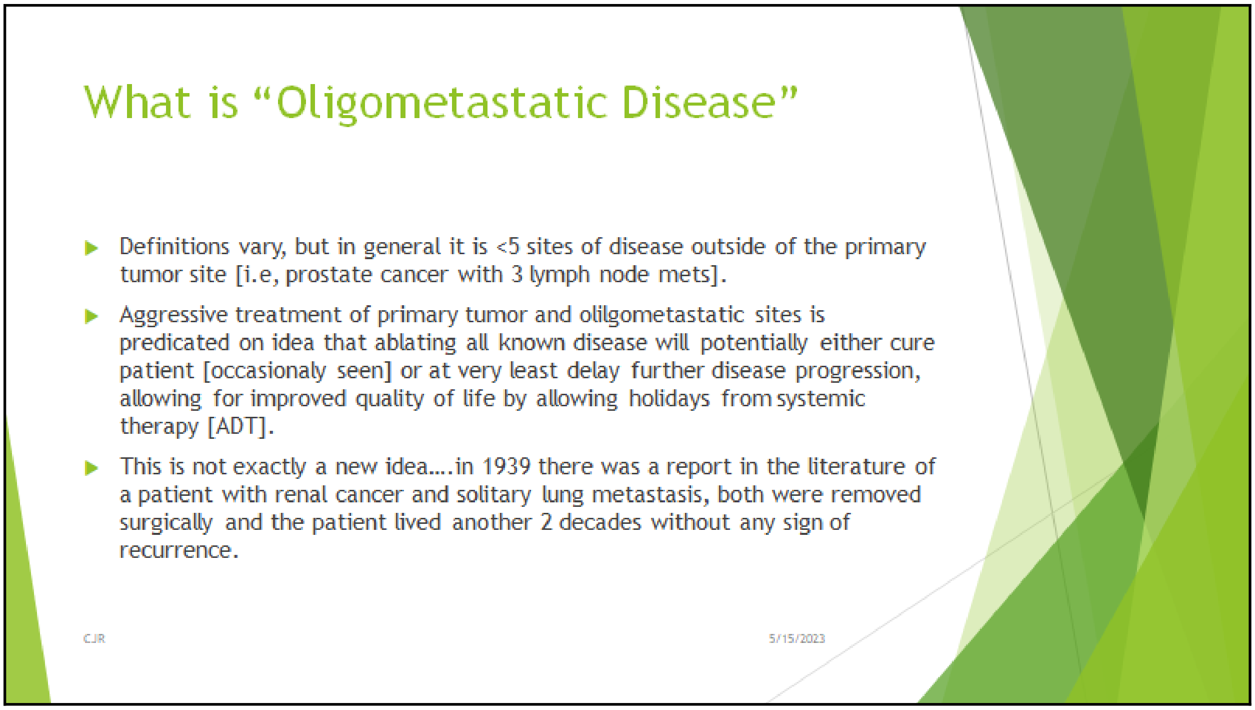
**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**




So I'll go to oligometastatic prostate cancer in the last couple of slides here.

**Metastasis Directed Therapy (MDT) for Oligometastatic Prostate Cancer**

As our technology has improved [advanced imaging such as the current leader PSMA PET] to identify this and as our ability to control systemic disease has also improved. This has become more of an issue, particularly because many of these patients have had prior treatment to some of these sites where they're having recurrence. So like so many things in medicine, it's an evolving story.

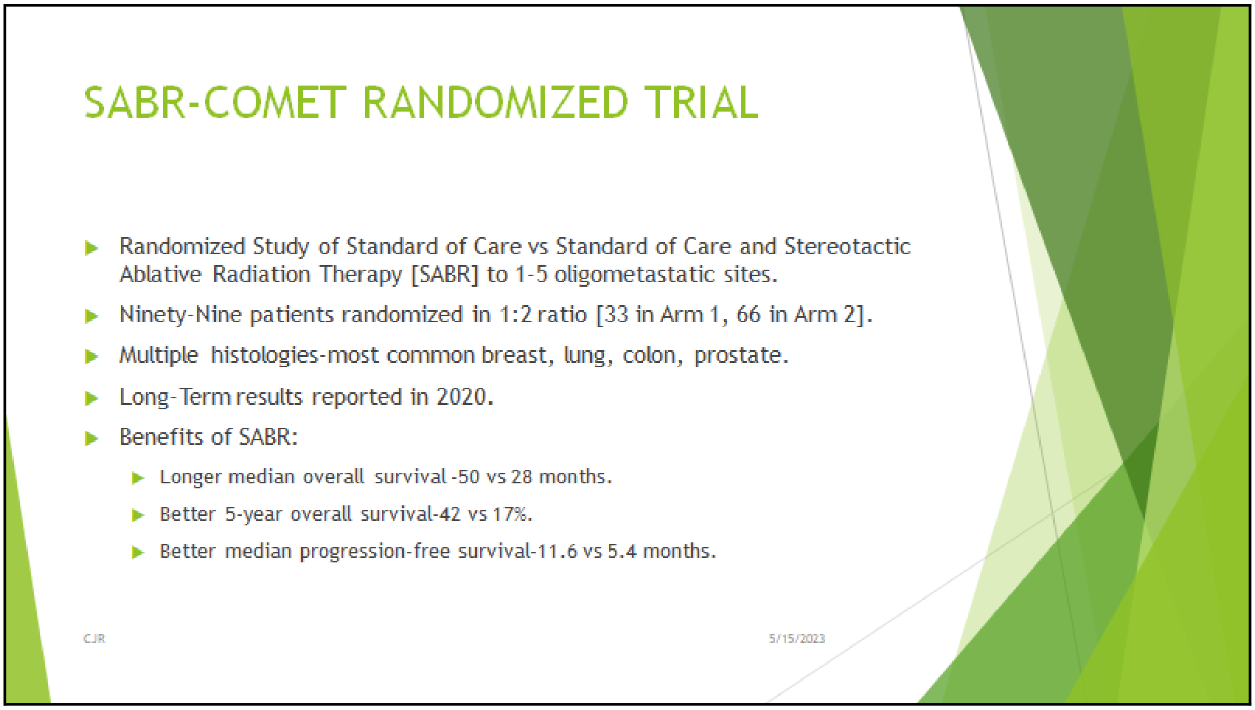



There are lots of different definitions that you'll see for oligo metastatic disease. One definition is five or fewer outside the primary tumor. So a prostate cancer with 3 lymph node metastases would be considered oligometastatic. The concept of oligometastatic disease is that there is a limited, earlier metastatic state, that if aggressively treated by metastasis directed therapy (MDT) and all known disease is ablated, there is the promise of cure and if not cure, at least a delay in further progression, improving quality of life including possibly allowing one to stay off hormonal therapy (ADT free survival). And if you ablate all disease you may have a chance at cure and you do see it 25-30% of time.

[Allen Morris: at 25:20 in the recording, I believe Dr. Rossi states that you see a cure in 25-30% of OMPC patients with totally ablated disease — I have never heard this before. Did he really say that?]
https://doi.org/10.2967%2Fjnumed.121.263684

This is, like so many things in medicine, not a new idea. You can go back and look in the literature, 80 plus years ago, and see reports of this. For example, concerning a 1939 case report of a renal cancer patient with solitary lung metastasis, who had surgical removal of both the primary (nephrectomy) and the lung metastasis (metastasectomy), and then lived another 20 years without any sign of recurrence. This oligometastatic concept got lost in the 80s and 90s, when I was a resident and even as an attending. If you got one metastasis, the theory was and still largely is, you're going to have metastases all over the place [the cow is out of the barn; no use closing the barn door/doing local therapy]. So we're not going to bother doing local therapy. Thankfully, researchers revisited that, and found that there is a rationale to do it. There are a bunch of trials that have looked at this.

## “Developments in Radiation for Cancer Care” (Carl Rossi) [#57]




This one that got a lot of press a few years ago. It was called the SABR (Stereotactic Ablative Radiotherapy) COMET trial.
DOI: 10.1200/JCO.20.00818 Journal of Clinical Oncology 38, no. 25 (September 01, 2020) 2830-2838.
*JAMA Oncol.* 2022;8(11):1644-1650. doi:10.1001/jamaoncol.2022.4394

Trials frequently have a really cool name (acronym), something catchy. ORIOLE (Observation vs. stereotactic ablative RadIation for OLigometastatic ProstatE Cancer) was a randomized study of standard of care, which was hormonal therapy, versus standard of care plus stereotactic radiotherapy to ablate in prostate cancer patients only.

In the SABR-COMET trial patients had one to five oligo metastatic sites, and they did this in multiple cancers, not just prostate cancer. The most common cancers in the study were prostate, breast, lung, and colon. They found patients benefited from SABR treatment. First of all, there were a lot of patients who were treated aggressively and had a longer median overall survival. So their median survival was 50 months versus 28. They had a better five year overall survival and a better progression free survival. So it's win win win. Right?

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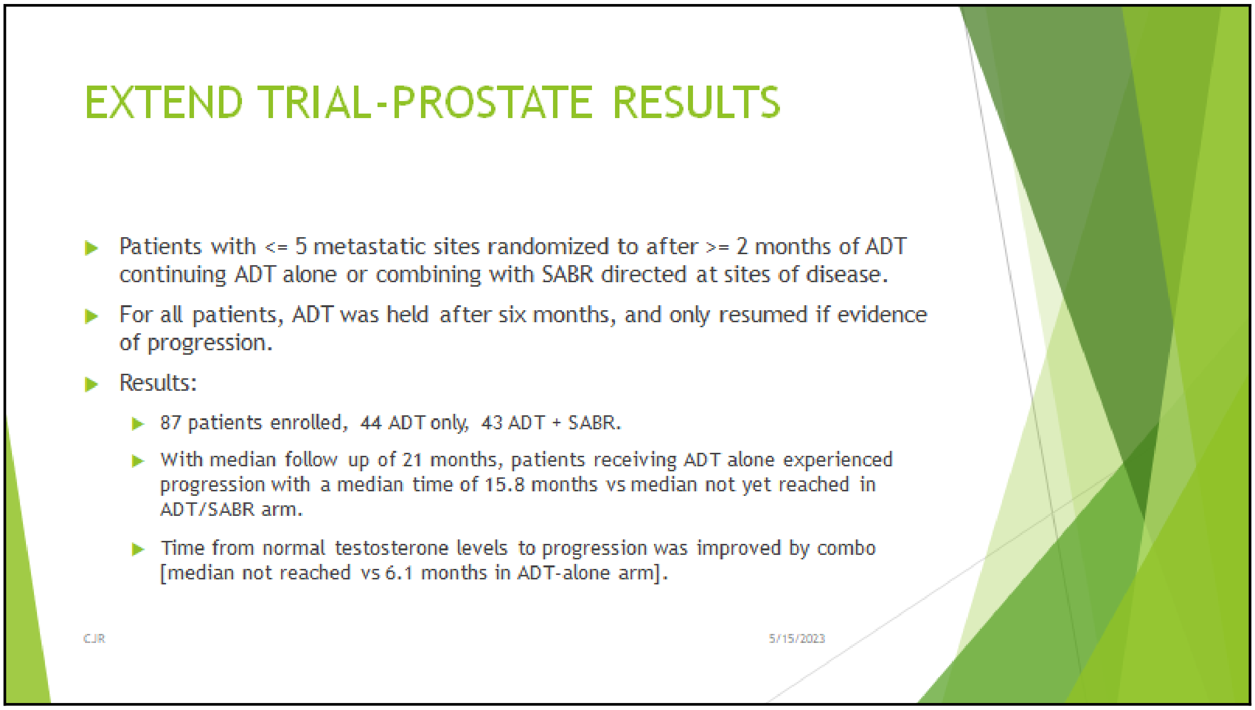


There was another trial that just looked at prostate cancer with, same thing, five or fewer metastatic sites, randomized after two months of hormone therapy to staying on hormone therapy alone, or combining the hormone therapy with SBRT to the sites of disease. And then you stopped the hormone therapy at six months and watched. And what they found pretty much first of all the groups are evenly split. The patients receiving hormonal therapy alone had progression. Concerning the endpoint of biochemical progression, the median time of 15 months, versus when this was published, the median had not yet been reached in the arm treated with hormone therapy plus metastasis directed radiotherapy. And also, not surprisingly, the time from normal testosterone levels to progression was improved by that combination. So what you found was that in the hormonal therapy alone when you stopped it, if the patients had normal testosterone levels, they progressed (BCR) within six months, whereas if you had received this combination therapy, they hadn't reached that median time to progression yet. So you're knocking their disease down while you're letting the patient have normal serum testosterone for quality of life.

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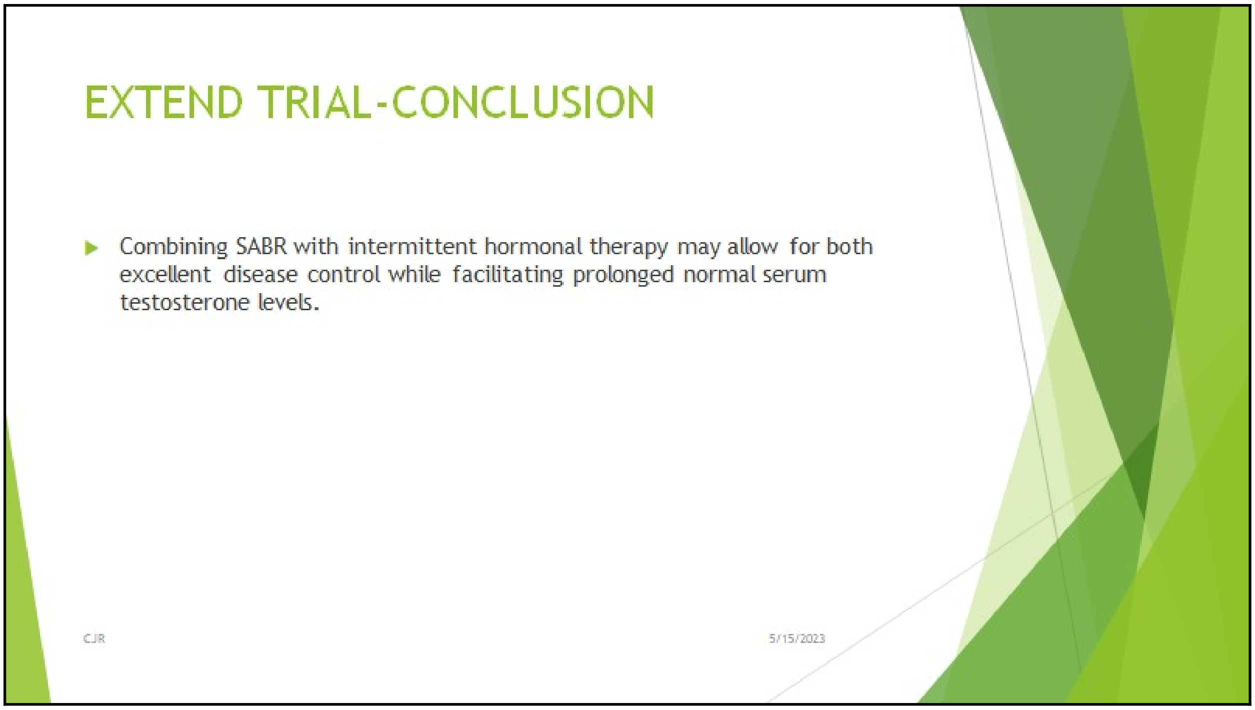
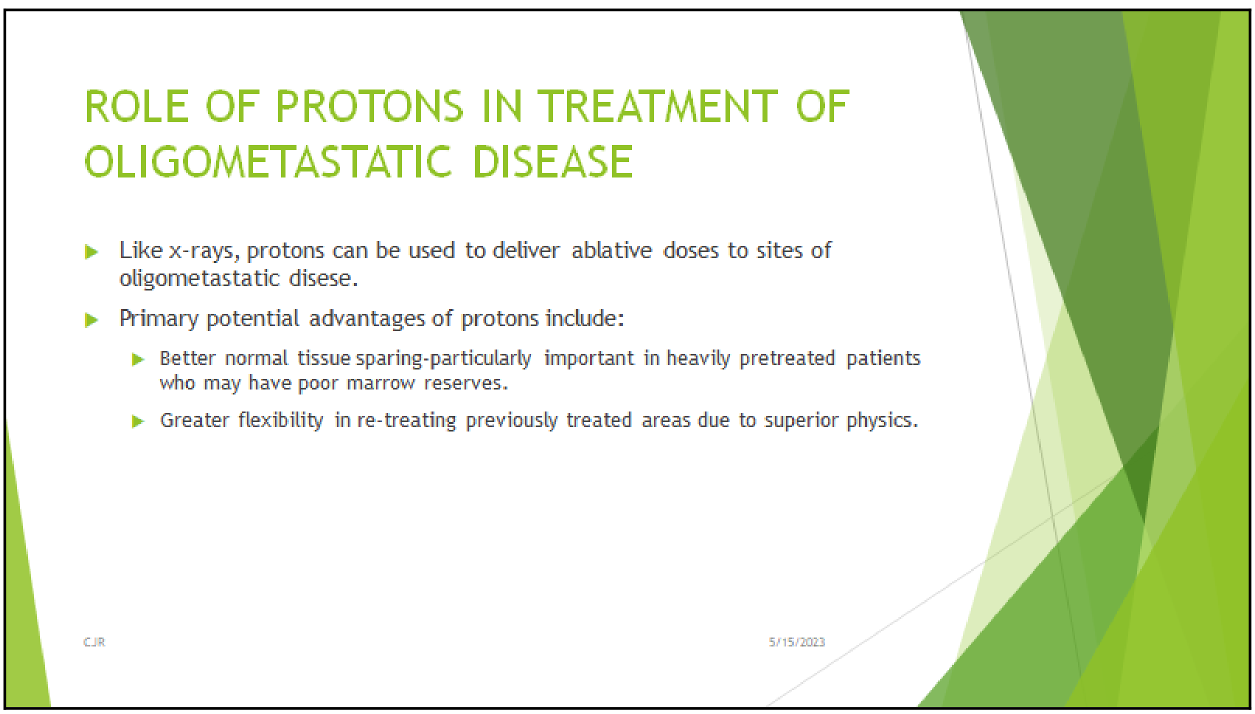



And that was their conclusion: that you get excellent local disease control and prolong normal serum testosterone (ADT free survival); so prolonged, relatively normal quality of life.




Where the protons fit into this: Protons are just one of the many ways that you can deliver ablative doses to these areas. The primary benefits of proton therapy go back to the physics. First of all, a lot of the folks that we treat have been heavily pretreated, including things that can cause cyto depletion of the bone marrow, like Pluvicto. And that's one of the downsides of IMRT ends up in other structures (Organs at Risk) such as bone marrow, liver, etc. So if you've got poor marrow reserves and you go around treating more marrow to radiate these oligo metastatic sites. That hurts your already compromised marrow. Proton therapy has a greater safety margin allowing one to give additional treatment. Again, because of our superior physics. The cancer cells could care less what you're hitting them with. They don't know protons versus X-rays. It's what you do or not do to the surrounding tissue (Off target toxicity to Organs At Risk) that makes the biggest difference.


This is fairly typical. Here is a patient I treated a couple months ago with a solitary rib metastasis. That's what you see here on the right hand side of the image. And I just used a Proton plan to give 30 Gray in five fractions (= 6 Gray per treatment session) to the rib metastasis. The plan spared the vast majority of the normal lung and all the other surrounding tissues. So it's a real quick treatment. The toxicity is effectively none. I think the most significant toxicity short term is that patients do get a bit of a skin reaction that occurs a week or two after the finish. And that's it.

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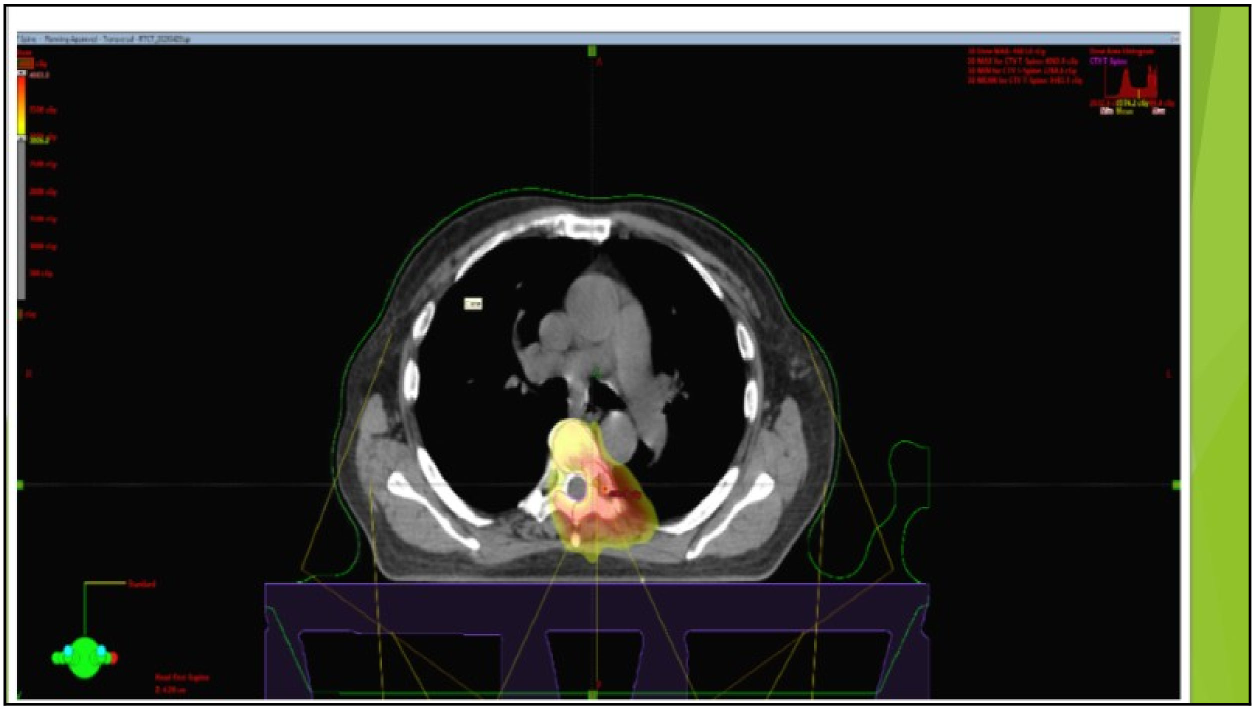

This is a case I'm currently treating in the Proton center right now, a gentleman, heavily pretreated. The patient initially had a prostatectomy. He then had local failure in the prostate bed treated with post operative radiotherapy in the bed with protons. Now he is oligometastatic and has undergone all sorts of systemic treatments, including Pluvicto, which was kind of moderately successful but unfortunately did a really good job of horribly affecting his renal function. His glomerular filtration rate (GFR) is really poor. And he is now oligometastatic with disease in a couple of areas. This is an area: T6 vertebral body with disease. And so the challenge here is how do you get an ablative dose into that and spare this thing right next to the vertebral body which is called the spinal cord. So we're able to create a plan with a hole in it. And that's what you're seeing here. So this is another five fraction plan with protons using I think four beams, where I'm giving 35-40 Gray to the metastasis in five fractions, a very nice ablative dose, and I'm not radiating the spinal cord, because I'm able to shape the beams and stop the particles before they get to the cord.

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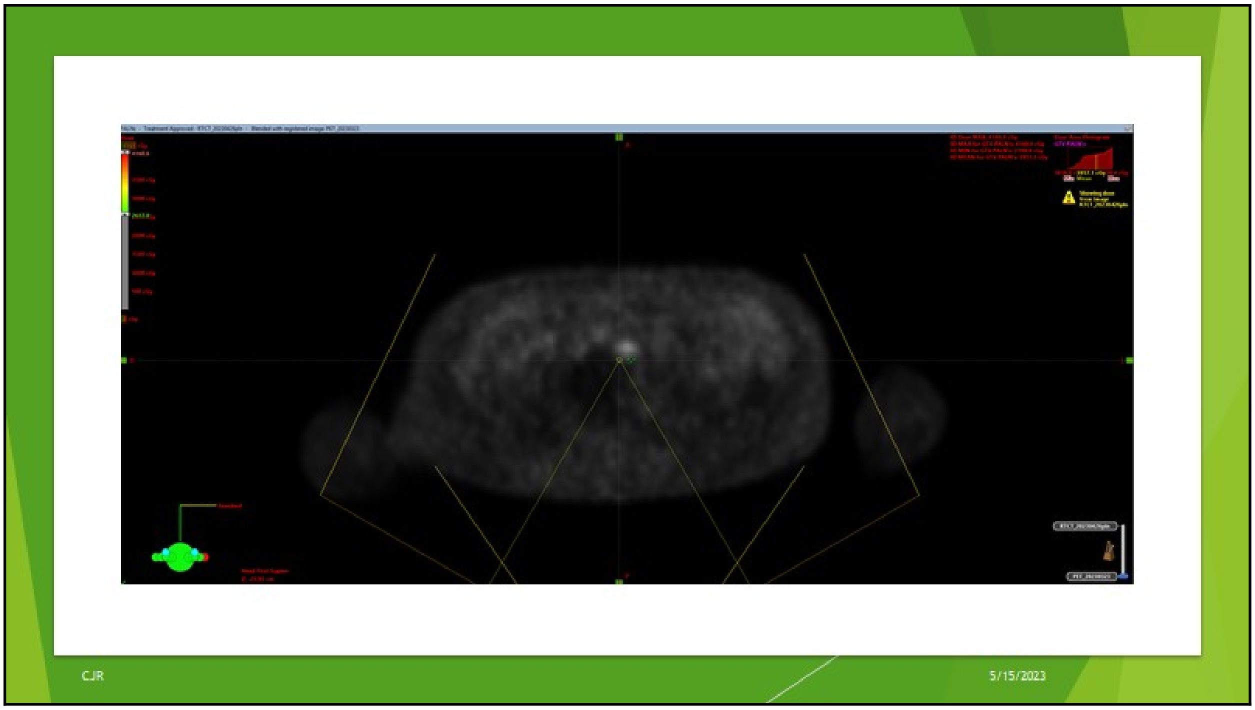
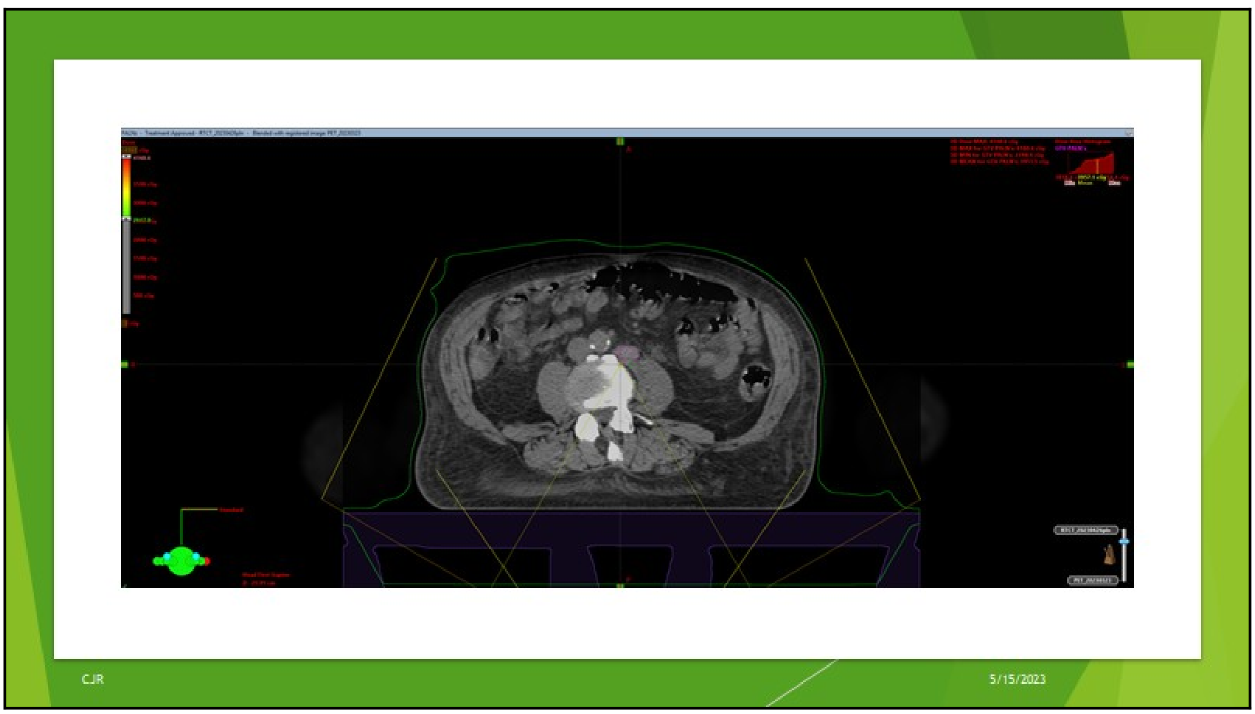



And the same patient’s most recent PSMA  PET scan shows a positive para aortic lymph node.




And you can see it outlined on my CT plan where I fuse the two (PSMA PET and CT) together,

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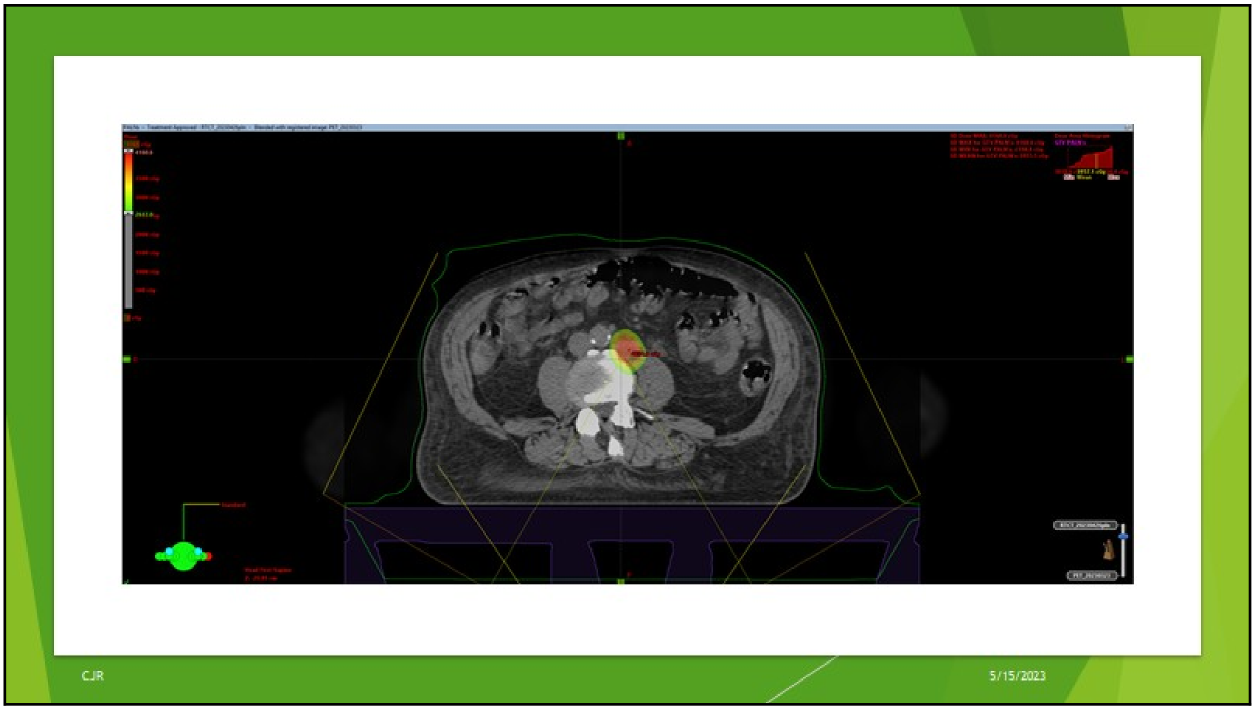



It's this area outlined in red that may not stand out too well. But that's what I'm doing. Again, we're treating this area at a high dose, and we're not treating, that's all that stuff you see in front of it, which is intestine, and we're not treating that thing behind it, which is a lumbar vertebral body. So we're able to treat these areas effectively with a lower probability of harm than you would get if you were treating this with X-ray, stereotactic X-rays (IMRT), where you'd have dose coming in the back and the front and those coming out the front and the back.

## conclusions

- Particle Therapy is no longer “boutique”, equipment is available from numerous manufacturers and becoming less expensive.
- This will, in fashion analogous to introduction of Cobalt 60 and Linac, lead to increased utilization and optimization.
- Particle Therapy is still in the process of adapting commonly available tools in modern radiotherapy but this process is fortunately well underway.
- We ultimately need to get to the point that the cost to the payor of delivering particle therapy is similar to cost of x-ray treatment.

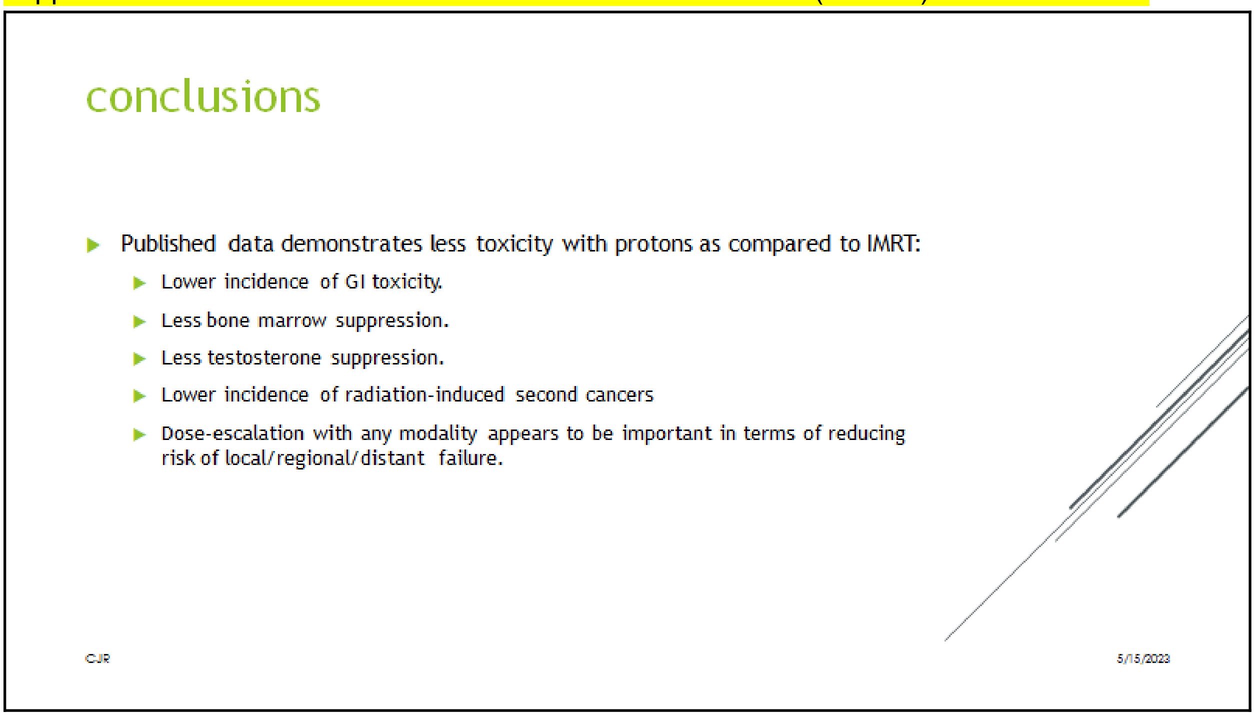
CJR 5/15/2023

**“Developments in Radiation for Cancer Care” (Carl Rossi) [#57]**

**More Proton Centers**

It's fair to say that particle therapy is no longer some boutique treatment that is only available in one place or two places in the world. We've got all these different manufacturers that are making the machines, including companies like Hitachi, and as a consequence machines are becoming less expensive. This is analogous to what happened in radiotherapy in the early 60s when cobalt 60 was introduced and then what happened with IMRT. We are still developing the ability to use our common planning tools that are used all the time with X-ray therapy. But that's really no longer much of an issue. And ultimately, you want to get to the point that the cost to the person who's writing the check for this treatment is similar to the cost of X-ray (IMRT) therapy. And we're actually almost there. That part makes the biggest difference in terms of acceptance. When this stuff costs more, insurance doesn't want to pay for it unless you can show them all some really good reason. When it costs the same. They don't care what you do. The insurance companies tell you to do whatever you think is best medically, we're going to write the same check anyway. So you can do what you see fit.

So in terms of the published data, what it shows us, not too surprisingly, protons are less toxic; suppress less bone marrow and have less effect on the bowel (GI tract) and the bladder.




I didn't mention it, but there are papers showing that we're not suppressing testosterone**.**

[Allen Morris comment: I think Dr. Rossi means greater ADT free survival?]

When we radiate the prostate, which is something that happens with IMRT. You heard about the second cancer risk. I think it's important to realize that higher doses with whatever modality that you have available are important because they not only help control the local disease, it can also help reduce the risk of disease showing up elsewhere in the body.

Brian McCloskey 33:57
I'm sure there are some questions. Thank you so much for a great presentation. I know it's going to be very beneficial to our community.

I want to just mention my case briefly, which is that we met last week I went through the entire mapping process using CT plus MRI and did the overlay with Dr. Rossi in the past it and I had previously seen salvage radiation and I had a little bit of a nasty lesion that was intermesh with my bladder wall and compressing my urine or the point is is that after we looked at the imaging, Dr. Rossi felt that I actually was not a good candidate. So I mentioned that because, you know, using this advanced imaging helps to avoid toxicity helps to avoid damage and as patients who've gone through multiple treatments, ruling treat Hands out is just as valuable as really treatment in. And so I want to thank him for, you know, his judgment that I trust him completely.

Carl Rossi 35:10
That's a really good point that sometimes the best thing to do is to not do something or not to intervene in that situation. It wasn't an issue whether I could technically get a dose in. I certainly could. But Is it helpful? And does the benefit outweigh the risk? That's a physician judgment call. Thankfully, it's not something that AI has spitting out, “saying yes or no” yet. But having all these tools lets you make those judgment calls with a greater degree of certainty. Or at least you feel better about what you're about the recommendation you make, because you have been able to do the analysis that can help to shed some light on what are the pros and what are the cons of this potential treatment?

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Amit Gattani 36:05
I kept coming up with questions to ask and you kept answering them before I could ask; very interesting. I am one of those who has gone through quite a few radiation treatments actually. Not to the prostate but to the lumbar spine, thoracic spine, skull base and femur, and it was SBRT and VMAT. And I have seen a lot of bone marrow suppression. Because of that, I am kind of curious if there is quantitative data on the toxicity difference between VMAT and Proton therapy? When you say that proton therapy is significantly better, is there quantitative data on toxicity to support that?

Carl Rossi 37:00
I'd say semi quantitative, you can outline the marrow space. And you can use that to decide how much radiation am I giving to the marrow space with one technology versus another. But that doesn't always directly correlate to the amount of bone marrow suppression that you create. Part of it has to do with how you outline what looks like marrow space, but it may not contain a lot of functional marrow, for whatever reason, as it gets replaced by fat or marrow stores change as we get older and stuff. So for adults at least, it’s a bit of an assumption. Although there have been a couple of recent papers that have looked at this, and compared say, doing what we call cranial spinal radiation, where you're treating the entire brain and spinal column and adults, which we do for certain metastatic cases.

There was actually a randomized trial at Memorial Sloan Kettering between doing this in breast cancer patients with metastasis to their cranial spinal axis, randomized between Protons and X-rays. This came out in the last couple of months. They found a very, very significant difference with the ability of patients to tolerate that treatment when favoring the proton arm, but also a difference in disease free survival because of it. We do it all the time in kids, because a lot of the kids that we treat, are also getting multi agent chemotherapy. So for treating their neuro-axis we stopped the beam before it goes into the vertebral body, and we're able to get the kids through the chemotherapy because the marrow is not being ablated. So it's semi quantitative. For example, in the vertebral body in the cervical spine alone, they usually don't contain a lot of marrow anyway. If you look at where an adult's bone marrow stores are, 25 percent are in the pelvis, and there are 25 percent in the lumbar spine. Then you've got the remainder being primarily in ribs, skull and to a lesser extent, the thoracic vertebral body. If I'm seeing a patient where I have to radiate lumbar spine, it could be a big difference. If I'm seeing one where it's treating the C spine, you're going to spare some marrow, but you're not going to see any clinical differences.

Amit Gattani 39:27
No, I went through pelvic and lumbar spine radiation as well.

Just a follow up question, you talked about the secondary cancers. Obviously, we avoided all my kind of soft tissue and organs and stuff in the radiation treatment, but I have developed a neuroendocrine component in addition to adenocarcinoma. Have you seen secondary cancer being neuroendocrine?

Carl Rossi 40:02
No, I haven't. It's certainly something people have talked about in literature. The usual secondary cancers from radiotherapy, whether it's protons or X-rays, when you're treating the pelvis you worry about leukemia because of bone marrow exposure. That's more of an issue with X-rays, of course, and you're worried about solid tumors, rectum, bladder, and soft tissue sarcomas. So, whether or not the neuroendocrine component is because of the prior radiotherapy, the prostate cancer represents an evolution or a devolution of the prostate cancer. It is a subject, where there's a fair amount of controversy. I'd say that the majority of opinion is that this is just a change. It's not a radiation induced change in the malignancy that has happened. It's something that happens, as the malignancy continues to grow, and you get more and more variation in the type of cells that are being cranked out.

Kerri 41:01
I have two sets of questions. One of them is: About 10 years ago at patient conferences, I remember, folks were mixed about proton therapy. There was evidence of high cost, and a lack of evidence of superiority. So I was curious, whether the efficacy – if there's something about the technology that's improved [since then], or if it's just that you have more data now?

And then my second set of questions is also from the patient perspective, when you're looking at making treatment decisions. We know, for instance, that MR-guided radiotherapy - i.e. the MRIdian system - is different from CT-guided, which probably your IMRT studies are focused on. So can you talk about: Are there any head-to-head studies, whether controlled or observational, that pit proton therapy against MRI guided radiotherapy? In terms of especially probably greater access right now for patients to that system than proton? So if you don't mind handling both of those questions? Sorry for the complexity.

Carl Rossi 42:09
A decade ago there were concerns over the cost, and that there was limited evidence on the efficacy, or superiority. I’m happy to talk about the answer to all this stuff. First of all, realize that when you talk about cost of treatment, that's not a medical issue, per se, that is a contracting issue. The reason I bring that up is because of a couple examples. First of all, we have contracts here at our facility with insurers, where the cost of doing a course of proton therapy for prostate cancer is no different than the cost of doing X-ray therapy. That's a contractual agreement that you make. So you can do this with a lot of different sites. It's not because while the technology is inherently more costly, it has more to do with the business practices that you're able to establish. There are some sites where it actually costs less to treat with protons because you can treat in a faster manner. The cost of radiotherapy is also determined by the cost of the number of fractions that you give. So when I have discussions of costs, when people talk about the high cost of proton therapy, they're often people who don't have any idea what the charges are for the treatment that they're delivering. I've had people tell me about the high cost of protons and when I tell them: “Do you realize that if you do IMRT - which is the standard, right? - that to Medicare, IMRT is 270% more expensive than 3D conformal which it is?” There were never any prospective randomized trials, showing that IMRT was more efficacious than 3D conformal, but it costs 270% more and they’re like “Really?”. Yeah, that's the truth. There were

no randomized trials, and it costs more, but we did it because of the physics. That's the same reason why we look at proton therapy, in terms of efficacy, superiority. We've been on this road in radiotherapy for 100 years, that every time you improve your technology and get more specific with where you treat, it's beneficial to the patient using whatever technology you have.

To say we have a lack of efficacy, where's your efficacy for your existing technology? You did that, you put in IMRT, you put in VMAT, because the physics was better than its predecessor, not because you did all these randomized Phase 3 trials to show that confining higher dose to a smaller area is better to the patient.

There's a great lecture by Herman Suit back about 20 plus years ago that talked about all of this. As the machines become more manufactured, cost has dropped. A one-room proton facility right now runs around $10 million. Not cheap. But if you look at a modern X-ray therapy center, especially if you're talking about using MR-guided machinery, the cost is getting to be pretty close! And those machines aren't nearly as long-lasting. Proton cyclotrons and synchrotrons last 25-30-40 years. Your typical LINAC has to be refurbished every 3-5 years, and that's often a multimillion-dollar process. Your second question was about whether or not we have any head-to-head trials yet of MR-guided LINACs versus proton therapy? The answer is no. And there's actually very limited data on MR-guided versus CT-guided radiotherapy. There's the one trial - the UCLA paper that came out a couple months ago - which first of all, it's physician-reported toxicity, which all of us physicians realize that we tend to underestimate our toxicity. That's just the reality; that's why I try to do patient-reported quality of life.

But the other thing in that study was that they said, “Well, you're able to use tighter margins, because we used MR guidance.” Well, you can use tighter margins with CT guidance, especially with fiducials. So whether that's showing that the MR is giving you superiority in terms of toxicity because you’re using MR guidance, or because they cut the margin from four to two millimeters, is - That question is up in the air. There are certainly advantages to MR guidance. And to me the advantage of doing it isn't so much that you're seeing the soft tissue, it's that you're eliminating yet another source of ionizing radiation exposure to the patient! (Which you don't want to do!) And it's not a coincidence that MR-guided proton therapy is also under development. The issue with doing it in the proton world is that it's gonna be technologically much more difficult. Because we've got magnets galore in our treatment rooms. And we’re doing all of our beam shaping electromagnetically with these big-ass magnets <laughs>. And if you have an MR in there for imaging - and people have done papers on this - you can start moving that little spot that you're using to paint with. It gets distorted because of these extraneous magnetic fields. So we want to develop it, and it will be in development. But again, I think the primary advantage is not because it lets you get a tighter margin or do something else. It's because it eliminates yet another potential source of toxicity, namely ionizing radiation for imaging.

Kerri 47:21
Well, I'm a fan of all those principles. Thanks so much.

Jonathan Starr 47:34
For salvage treatment of the prostate bed, or after recurrence after say, prostatectomy, does proton beam radiation do less damage to the pelvis and to the bone marrow than IMRT. Although it's too late to benefit me, what happened in my own personal case was I had recurrence right after prostatectomy. I did get IMRT to my prostate bed and full pelvic IMRT. I had substantial reduction in my white blood cell counts, especially lymphocytes. They went down to like a third of the bottom of the standard range. Now, after a number of years, some of those neutrophils, lymphocytes, and monocytes have recovered to the normal range after five years. But I just wonder sometimes what would have happened if I had known about proton beam treatment? I wonder what to tell other people in support groups about it, in regards to full pelvic salvage radiation?

Carl Rossi 49:12
The general rule when you're looking at comparing the proton plan of anything to an X-ray plan of anything is that the larger the field and the more irregular the shape, the greater the advantage is going to be to use protons versus X-rays because you're covering an area like the whole pelvis and the lymph nodes, which are along the blood vessels. That's a big field to treat with X-rays. And even though you can concentrate very beautifully on the lymph nodes and prostate, you have a dose bath and that dose bath is primarily going to be to the iliac wings, which is where you have to have your pelvic marrow. So if you treat that patient with protons, rather than having a dose back to the iliac wings, the way you treat the pelvic lymph nodes, is you bring in a single posterior field which effectively is in the shape of a U because that's the way lymph nodes are distributed. So you stay away from the iliac wings and the iliac wing radiation dose is zero. So you're sparing bone marrow and the iliac wings. The other thing that you're sparing is the intestine because that's anterior. And that's in the center of the U with a dose of zero. You're sparing the majority of the bladder, because you're treating with much more direction where the majority of bladder is not receiving any radiation. That's where you would see the differences, bone marrow exposure and exposure of bowel and bladder to radiotherapy, there would be no difference in the dose to the prostate. But you can do a very nice job of sparing normal bone marrow and normal intestine and normal bladder. Great, thank you.

Richard Anders 51:21
I just wonder if proton beam therapy is being used at all for bone marrow transplants?

Carl Rossi 51:41
We've talked about it, but we haven't done it partly because of the field size. So if you're going to do a condition, a patient or a bone marrow transplant, you already have to treat your whole body because you have to plan all the marrow. And while you can do that, with the scanning beam, it would take a while. It's been something people have theorized. But as far as I know, it has never been done in reality.

Richard Anders 52:04
I guess maybe you could do it in sensitive areas. Stay away from the eyeballs or your heart.

Carl Rossi  52:10
The idea is that you can do it and spare a lot of healthy tissue. If you look at the toxicity from whole body radiotherapy, that you're doing prep for a transplant. The lungs are a big issue. So theoretically, you could treat the risk of gastric ribs and you got to treat the thoracic spine. And you can stop the beam before it hits the lung, although protons, they stop in the lung but because the lung is so low density, they don't stop nearly as rapidly as they do in soft tissue. We've had some patients that have needed whole body prep for bone marrow transplant. Many of us have gone from Europe to the City of Hope,because that's one of the few places that still set up to do it.

Richard Anders  52:53
Yeah, really, for young women. I think the biggest case – and I have a personal experience with this – was for reproductive organs.

Carl Rossi  52:59
Yeah, right. And this is also an issue in pediatrics. A lot of the stuff we treat in kids are central nervous system tumors where you're treating the whole neuraxis, that whole brain and spinal cord, and you're stopping the beam. So it never hits the ovaries or never hits the testicles. And that's why we know at any one given time, probably 15-20% of patients we're treating here, just remote proton centers are kids.

Richard Anders  53:27
Thank you.

Jeff Krolick  53:34
A few years back. My oncologist had recommended radiation. I'm in the oligometastatic category. And we did this with Dr. Tran, who was then at Johns Hopkins through IMRT. And during that time, I was encouraged to be on a ketogenic diet. I guess, in my experience, although that didn't put my prostate cancer into remission, I didn't seem to have any noticeable side effects from the treatment. I'm wondering if you're familiar with any research about either diet or other things that can be done to mitigate possible radiation side effects from that kind of treatment.

Carl Rossi  54:59
Yeah, the short answer is my familiarity with this is pretty minimal. I think the question that typically comes up is, “is there a diet that can help with my prognosis?” And that's where I get back to Mark Moyer ads, if it's good for your heart, it's probably good for your prostate. There certainly are things you can do from a dietary standpoint, especially if you're getting X-ray therapy to the pelvis, that can minimize toxicity. Because what it has to do with effects on the intestine primarily. So if patients are eating a diet, where they're going to have anything which would normally make the stools loose, so roughage, it's going to be that much worse, if you are getting radiotherapy to the pelvis. So we often have them change to a diet if you're giving pelvic X-ray therapy that is less likely to cause diarrhea. I don't know if the specifics of a ketogenic diet

would make that much of a difference in what I do. You know, we rarely see any GI toxicity at all during this because you just did the radiation dose of the intestine is zero, so you're not worried about it.

Jeff Krolick  56:10  Okay, great, thank you.

Allen Morris  56:20
I just wanted to thank Dr. Rossi for the informative talk. But more importantly, I wanted to thank him for being my doctor. You may not remember me, Dr. Rossi; but in June 2020, 3 years ago, you treated me for oligo recurrent metastatic prostate cancer involving three bone Mets. And I really appreciate you taking me on especially since Pylarify (Dcpyl F18-PSMA Pet, next generation imaging) which detected my 3 bone mets was not even FDA approved. In fact, as you know, Pylarify would only be subsequently approved 1 year hence, June, 2021.

[Allen Morris note: I was actually also in the study trial at UCLA for Gallium-PSMA PET. So, believe it or not, I got both next generation advanced imaging in a trial. I was one of only 27 patients that got both at the same time. And though, via comparison in this small group, Pylarify slightly outperformed gallium scan; the conclusion was that their performance was comparable and the conclusion was both were disruptive compared to standard of care: bone scan and CT scan, disruptive by several orders of magnitude.
Curious, I was the only one of the 27 for whom there was total discordance. The Gallium scan did not pick up any of my 3 bone mets whereas Pylarify did. The latter analysis presumes that Pylarify is the gold (truth) standard; a faulty presumption.]

**Key Quotes by Dr. Rossi (Allen Morris)**

“Just to remind folks, the target for radiotherapy is DNA. That's what we do with any type of radiation. What we're doing is we're causing DNA breaks.”

“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.”

“People will say, “Well, it's low dose.” You have got to put that in context. When you are giving 8000 rad to the prostate, you are unnecessarily giving 3000 rad to the intestine, and that's not a low dose. In fact, that's a very high dose to normal tissue. But when you're using X-rays, this is what you're stuck with from the physics side, because you can't make the X-ray beam stop at a point in space.” “you have dose on the way in and dose on the way out.”

“The cancer cells could care less what you're hitting them with. They don't know protons versus X-rays. It's what you do or do not do to the surrounding tissue that makes the biggest difference.”

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Pencil Beam Proton RT: “Effectively, it's a 3D printer. You're painting dose and layers, a millimeter thick, through your target. So you can put high doses in some spots, lower doses in other spots. That's going to be important.”

“Proton patients had second cancers at less than 1/3 the rate that was seen with either type of X-ray therapy.”

**Key Take-Away Messages (Allen Morris)**

1. Proton therapy has an advantage over X-rays (IMRT, SOC) and that advantage is a radiophysics advantage.
2. The radiophysics advantage of Proton therapy is due to the Bragg effect. The Bragg effect has the promise of limiting Off Target toxicity, not only to the usual suspects, Intestines and Bladder; but also to the less recognized and underrated issue of radiation-induced secondary cancers.
3. There is no Level 1 evidence of a difference in target efficacy. Proton and IMRT are equivalent in efficacy.
4. Both Protons and X-rays (IMRT) have the same mechanism of action: causing DNA breaks including the most toxic dsDNA breaks. Cells do not care which modality is used.
5. Double strand DNA breaks are a two edged sword, on the one hand they “overwhelm the cell's ability to repair that damage, so the cell dies when the cell attempts to replicate” - apoptosis and on the other hand if the cell does not die, RT causes genomic change, including uncommonly into a radiation-induced second cancer
6. Proton patients had second cancer incidence less than 1/3 the rate that was seen with either type of X-ray therapy.
7. There is a memorial in Hamburg, Germany to pioneering radiation scientists who died from radiation, mainly radiation induced cancers.
8. Despite the foregoing Proton advantage, IMRT is still and will be for the immediate future, the standard of care (SOC). Dr. Rossi lists the following obstacles to Proton therapy becoming Standard Of Care (SOC)
    a. Limited Access - Proton facility availability
    b. Limited acceptance by insurance companies, specifically cost disadvantage
    c. Limited head to head comparisons with SOC (IMRT) to prove Proton superiority, but Rossi says this standard was not applied to the acceptance of IMRT or VMAC
    d. Limited urologic community acceptance and public awareness which speaks to the concept of adoption rates
    e. But Dr. Rossi says all of these obstacles are in the process of being overcome. Stay tuned.
9. Proton RT, though limited by availability, is an option if one is a candidate for RT; but a patient would have to know about it and specifically seek it out.
10. Also, stay tuned to the integration of both IMRT and conceivably further in the future, once the magnet issue is overcome, Proton therapy with MRI precision guidance vs. the SOC CT precision guidance with/without fiduciaries. The real time guidance that allows 1

mm accuracy around target structures and corrects in real time for positional changes. Note: planning target volumes are usually 2-4 mm to allow for patient movement, etc.

Note: The above discussed precision real time guidance is different from PSMA PET/CT or mpMRI gross planning guidance to oligometastases or tumors within the prostate and is currently available.

Dr. Kishan just reported on a randomized (Mirage) trial of MRI-guided real time guidance IMRT at UCLA. I believe UCLA, with the meridian system, is the only facility on the West Coast experimenting with this new modality. His findings suggest lower toxicity including in particular lower GI toxicity. I suspect Dr. Kishan would say this modality is as good as or better than Proton regarding off-target adverse effects.
https://www.urologytimes.com/view/dr-kishan-highlights-findings-from-the-mirage-trial-in-prostate-cancer