Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center and she is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. Yale Cancer Center Answers features weekly conversations about the most recent advances in the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation with Dr. Dave Carlson, an Assistant Professor of Therapeutic Radiology at Yale School of Medicine. Here is Anees Chagpar.

Chagpar Dave, tell us a little bit about what exactly medical physics is. A lot of us remember physics from high school, some of us not fondly. What exactly do you do?

Carlson For people that are not intimately familiar with radiation oncology, the field of medical physics is a little bit behind the scenes. My background is actually in the science of physics and all of us come to the field from the physics side of science and basically what we do is we help the radiation oncologists and the biologists in our department apply physics to treatments. So my undergraduate degree is in physics. I have a graduate degree in medical physics and the training in our field has been standardized over recent years. Now, we all go through residency programs in either radiation oncology, physics, or imaging physics. So we now specialize in different disciplines and essentially we are there for technical support as part of the team with radiation oncologists to treat cancer patients with radiation.

Chagpar So some of us, especially listeners of Yale Cancer Center Answers, kind of know what radiation therapy is, it is a therapy where you get radiation applied to a cancer, but what does any of that have to do with physics, what exactly do you do in supporting the team?

Carlson The technology behind radiation therapy is quite complex. If you think about conventional x-rays, this goes all the way back to 1895 when it was first invented by a physicist, Wilhelm

Röntgen, and back then, the energies were very low. So on the thousands of electron volt energy range. Now the technology has advanced to a point where about 60 years after the invention, we developed medical linear accelerators that can essentially accelerate these electrons up to millions of electron volts. So very high energies and that is based on accelerator wave guides but uses microwave injection. It is very complex technology. So what we as physicists do in the clinic, is we basically take care of these accelerators and we make sure that they are working correctly. We make sure that the radiation that is coming out of them is well characterized, and that we know exactly what we are treating the patient with the beams and the specifications. So on an ongoing basis, we are intimately involved with these complex medical devices. In addition to the technology side, we work with the radiation oncologist to identify a target. Where is the tumor that we want to treat? That is one of the bit questions and the big challenge in radiation oncology and that is the whole imaging side, imaging physics. So, how do we identify it based on anatomy as well as functional

3:40 into mp3 file http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3 imaging modalities. Once we have identified the target accurately, we work with the team of radiation dosimetrists to develop treatment plans that basically take what we know about our linear accelerators in terms of the beam characteristics of the radiation fields, and we develop very complex treatment plans, we can rotate that radiation beam around the patient, we can collimate it with different devices and basically calculate the absorbed radiation dose on a patient's specific basis to their actual tumor and that is a process that we work very closely with the radiation oncologist who works closely with the medical oncologist. So they derive prescription doses that we know based on empirical evidence how we want to treat certain types of disease and we basically help them treat to the prescription dose that they want treated to. Of course, once we develop this treatment plan, another large component of the field of medical physics is verifying that we are accurately delivering what we think we are. Because this is very complex technology, we actually are measuring the output on these machines regularly, we are checking how the radiation beam is changing and we are also on a patient specific basis we are measuring individual treatment plans, especially the more complex techniques, which we can perhaps talk about a little bit later.

Chagpar All of that sounds really complicated and I want to take it back a step so that we can understand all of these pieces that you laid out. Tell us the difference between x-rays, which is radiation, and getting radiation therapy, how are those different, or is radiation therapy just a lot of x-rays?

Carlson When we talk about radiation, what is radiation? We have radiation that is all around us right? The light that is coming out of that lamp up there is actually part of the spectrum of energies for electromagnetic waves. So basically we look at ionizing versus non-ionizing radiation. So if we have electromagnetic waves, as the wave length gets shorter the energy of the radiation increases and once we reach a certain threshold, where it can actually ionize atoms, that is considered ionizing radiation. So in diagnostic imaging and radiation oncology what we are dealing with is ionizing radiation. It is in the x-ray and the gamma ray part of the electromagnetic spectrum. So when I use those terms x-rays and gamma rays, there are basically two different ways to generate this radiation and we actually use these different techniques in our clinic. So the main one that I have talked about so far is the medical linear accelerator, this is a machine that you can basically plug into a power supply and you turn it on and off to generate your x-rays, but the other side of the equation are really the gamma rays, which we can also use, that come from radioactive material. So you can have unstable elements, basically they are decaying with a known characteristic rate and they emit these gamma rays. Now, we use radiation in imaging, we also use it in therapy, the dose that we use in imaging, the goal is really to keep them as low as possible. So we want to get useful anatomical and functional information about a particular part of the body or about tumor if it is a cancer related study. The goal there is to really use as little radiation as possible, but to get a good picture of what we are interested in. On the therapy side, it is the exact opposite. We want to give large enough doses basically to kill all of the disease while

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minimizing doses to the surrounding normal structures. So on the radiation oncology side, our job as medical physicists is really to help the physicians develop techniques that are going to specifically target cancerous cells while minimizing and keeping radiation off the normal adjacent tissues, and that has really evolved over the last 50 years in our field quite dramatically.

Chagpar One of the questions that some of our listeners may have is, there has been a lot of talk about getting too many x-rays causing cancer, but then on the other hand, you also have higher doses curing cancer. How exactly does that work?

Carlson We know that any dose of ionizing radiation has a potential risk for secondary cancer induction. Most of the epidemiological data that we have that looks at cancer risk for radiation dosage, it deals with the high dose range. So we have to make an assumption, a very conservative assumption, that when we go to very low doses that there is a linear extrapolation down to low doses. And the other thing to consider, this is a stochastic risk, so you are not going to get a dose and necessarily cancer, but it is a probability of getting secondary cancer induction and for imaging procedures, it is a very low probability. So the recent efforts in diagnostic radiology have been really to lower unnecessary radiation dose from imaging procedures. Certainly the medical benefits from the vast majority of imaging procedures that we are doing far outweigh the cancer risk associated with them, but we know even low doses do have a small potential increase in cancer risk. So that is the goal, to minimize the dose for the medical benefit and the image quality that we need to really diagnose and successfully treat a disease.

Chagpar And so that is another reason why when you are giving high doses for radiation oncology, you really try to target the tumor and not the normal tissue. Tell us a little bit more about how exactly you do that? Because the tumor presumably is surrounded by normal tissue, so how do you get your x-rays to go only where you want them to go and not anywhere else?

Carlson Let me start by backing up and going a little bit into the history of how the field has evolved because I think in the last couple of decades, the advances in our technology to keep dose off normal tissue has increased dramatically. If you go back to the early 20th century, people were already beginning to use x-rays therapeutically to treat disease. Now the problem, and I alluded to this previously, was that we were using very low energy x-rays. So in the thousands of electrons volt range and that basically deposited a lot of dose at the surface of tissue, so your skin reaction and the way your skin was damaged limited the treatment effectiveness. Once we developed this microwave based accelerator technology to increase that electron energy, now we can generate x-rays that are in the millions of electrons, which can penetrate much deeper into tissue. So that was one of the large advancements that happened in the US, and in about 1956 the first medical linear accelerator based on microwave technology was implemented. In the early days, they were treating with larger radiation fields, but from different angles. So when you got to the tumor that is where the doses all added up from the different beams that were coming in from different angles and in the 90s the big advancement, which is now sort of standard of care for a lot of disease, was

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intensity modulated radiotherapy. So, now from different angles we are treating with radiation beams but we also have very complex collimator made out of multi-leaves, so these collimators can move while the radiation beam is on. They can sculpt the radiation dose to the tumor and that essentially lets us increase the gradient of the dose from the tumor to normal tissue. So, we are basically keeping dose off those adjacent normal tissues while giving the highest dose to the tumor. That is on the treatment side and I mentioned before another one of the large problems that we are dealing with is how do we precisely know where that target is? Where the tumor is? We have all of the diagnostic imaging in advance that can be used for target definition, but on the treatment side, if we do not really know where exactly the target is and we are delivering these high radiation doses, we can have geometric misses. So, we essentially add margin to our target when we are treating. One of the other large advancements in the last decade or two has been imaging guided radiotherapy, so now on the treatment side as well, we are doing sophisticated imaging, 3D imaging, volumetric imaging, with the technique called cone beam CT. Before the treatment we can do a cone beam CT and we can accurately identify a 3D volume with good soft tissue contrast to basically position the patient on the table and increase our confidence in where our actual target is, and that allows us to reduce our treatment margins and also to keep more radiation dose off of the normal tissues.

Chagpar That is great, so you do the CT scan and you figure out where exactly the tumor is and you have all of these techniques where you can turn one beam on another beam off and have one beam going really strongly and another beam less strongly to help you to modulate the radiation, but what if somebody moves during therapy, how does that work?

Carlson Absolutely, that is a big concern and this starts from the pre-treatment imaging all the way to treatment immobilization and localization is one of our main priorities. We have wonderful radiation therapists that we work with, that are experts in this area that keep the patient as immobilized as possible while they are on the treatment table and that might work great in a large number of tumor sites such as in the brain, with rigid anatomy, but we also have locations where even if you have the body immobilized, you are going to have different areas of the body where motion is going to be a concern, such as in the lung. So, we have extra techniques that we can use in areas where we know motion is going to be a concern.

Chagpar We are going to talk more about all of these techniques and how medical physics helps us in radiation oncology after we take a short break for a medical minute. Please stay tuned to learn more about therapeutic radiology with my guest Dr. Dave Carlson.

Medical

Minute The American Cancer Society estimates that more than 60,000 Americans will be diagnosed with head and neck cancer in 2014. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments and in many cases less 15:15 into mp3 file http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3 radical surgeries were able to preserve nerves, arteries, and muscles in the neck enabling patients to move, speak, breath, and eat normally after surgery. This has been a medial minute, brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest, Dr. Carlson. We are talking about medical physics and radiation oncology and right before the break, Dave, we were talking about how you use imaging to figure out where the cancer is and then a whole series of complicated physics to figure out how exactly where you are going to deliver your dose to the tumor and not anywhere else. One of those was figure out where the tumor is, give yourself a margin and make sure that the patient stays really still. Are there other techniques that you use in radiation oncology that target just the tumor and not surrounding tissue?

Carlson When we talked about motion management and immobilizing the patient, I mentioned there are certain tumor sites where even if we have the patient completely immobilized from the table we know that the tumor is going to move, such as a lung cancer. So one of the things that we can do is a technique that is now clinically implemented in most places, called a 4D CT scan. So essentially we are looking at the external chest and the respiratory cycle, and we can acquire CT data over that entire respiratory cycle and then basically go back and bin respectively the data into different phases of the respiratory cycle. So that we can know where the tumor is throughout the breathing cycle, and that data can be used on the treatment side. So we know exactly where the lung tumor is during the radiation treatment and we can either increase our target volumes to make sure that we are always hitting the tumor or we could actually do active things such as gating the treatment, so we know over these particular phases of the breathing cycle, we can turn the beam on, we can turn it off when the tumor leaves that area. There are also people on the research side looking into much more complex ways such as taking these multileaf collimators that I mentioned before and moving those to sort of match the motion of the target.

Chagpar What about other things that you can do with breathing? Do you ever get people just to hold their breath and say, hang on, let us give you this radiation and then now you can breathe?

Carlson Absolutely.

Chagpar Without having them pass out?

Carlson Yes, and that is actually one technique that we are actively using in our clinic for breast cancer patients, so we know, for example, for certain cases that heart dose could be a concern and we know that if we look at the respiratory cycle, we may be able to target the tumor over certain phases of the breathing cycle where that will help us reduce say, cardiac dose. So we can basically ask the patient to breathe in deeply and treat when the heart is furthest away from the target.

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Chagpar That is really great. I guess another thing is, as you try to conform your therapy just to the cancer itself, you talked a little bit before about using other forms of radiation like gamma radiation. Tell us about how that works, I mean it is different then having the light switch on, you said that it was really particles that are unstable, how does that work? Is that still emitted through one of these linear accelerators or is that something that is implanted into people, are there different kinds of radiation?

Carlson We do use a lot of unstable radioactive material in our therapies and there are different ways that it can be done, for example, you could use cobalt-60 in an external beam configuration such as the gamma knife. We have a large gamma knife program at Yale where we have over 200 cobalt-60 sources that are sorted in half of a sphere and we treat a lot of cranial tumors with that. There is also a whole field of brachytherapy, which basically involves taking these radioactive materials, similar to the ones used in gamma knife, but instead of doing an external beam approach, we either permanently implant radioactive seeds in the patient or we can temporarily implant them. So high dose rate brachytherapy is one of the clinical programs that I am involved with that uses an Iridium-192 radioactive source, it has a lot of different potential applications and we treat GYN-oncology patients and we have a partial breast irradiation program. In that case it is either intracavitary or an interstitial application and we basically have a small radioactive seed on the end of a wire that we can basically connect to a specific applicator and we send that source out for a certain period of time, we have the doses very accurately calculated and then the source comes back out and the procedure is quick and relatively easy.

Chagpar How do you decide whether somebody is a good candidate for the seed versus some of these other techniques where you are treating the whole breast, for example, or the whole pelvis with external beam radiation?

Carlson That is a very complex question and that is specific to the disease site and it is specific to the patient and that is a decision that is made with the whole team, so the medical oncologist, the radiation oncologist and the patient, and for certain sites it may be much more of a clear choice than others. For example, with prostate cancer, permanent seed implants versus external beam radiotherapy versus proton therapy these days is a very hot topic of debate amongst patients and physicians and there is evidence I think for external beam photon therapy and permanent seed implants that we are getting approximately equivalent outcomes just in this specific example.

Chagpar So there are different types of radioactive seeds, you mentioned Iridium, are there other unstable isotopes too that you use and how do you pick between those? Is it that some of them give you more radiation and some of them give you less? How does that work?

Carlson I mentioned the prostate permanent seed implant example and there are a number of different radioactive seeds that are used such as Iridium-125 and Palladium-103 and they have different physical characteristics. So the gamma rays that are emitted from the nucleus of the radioactive atom have slightly different energies so that means corresponding to penetration depth so with

22:34 into mp3 file http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3 these permanent implants they have energies that are around 20 and 30 keV which means they do not penetrate very far in tissue and that is ideal for this kind of permanent brachytherapy implant. They also have different half-lives, and what a half-life is basically, if you have a radioactive material you know it is going to decay over time and interventionally it will decay to very negligible levels, or background radiations so that could happen over days, it could happen over months. So these are considerations that we have to carefully look at when we are looking at picking the best radioisotope for a specific application.

Chagpar Going back to our original conversation, you said that one of the things that a medical physicist also needs to worry about is actually checking to see whether the dose that you plan to give and that you were giving actually got to the target and how much got to the normal tissue. How exactly do you tell that?

Carlson This is increasingly important in light of the recent technological advances that have made our treatments much more complex we have moving collimators that change the radiation film during the treatment. We have image guided radiotherapy that we use to reduce our treatment margins in certain cases so really verification that what we are planning to deliver and what we actually deliver is very crucial and in these cases we are actually doing specific measurements designed in advance of the patient's treatment to verify what we are intending to treat is actually getting treated and we have many different techniques that can be used. We use ion chambers, we can use diodes, different types of radiation detectors, we have two dimensional rays that can give us a signal that we can compare to what we were planing to treat and there are even 3D volumetric based detectors that can be used. So basically for these complex treatments, the physicist in advance we are going on the actual treatment machine, we are delivering the actual treatment and we are measuring it physically with an independent device and we are basically saying, is this of sufficient quality before the patient actually comes in for their treatment?

Chagpar And then once the patient does come in for the treatment and you have done all of this prep work and it seems to be perfect, is there a way to double check and say, how much did the patient actually get?

Carlson Absolutely, there are a number of different techniques and we call this in vivo symmetry. So instead of in advance of the patient coming we are actually going to be doing measurements with the patient in the room and this is not done for every patient, it is done for some of them in certain cases. We have things called thermoluminescent dosimeters, they are little crystals that have a signal when we deliver a dose to them, and we can basically heat them and get a live signal that comes off and we can relate that to the delivered dose. We have diode detectors that we actually can put on patients in real time that can give us a reading of the dose. So when we treat, for example, a total body irradiation patient that we are giving very high doses to the entire body, this is pre-bone marrow transplant, what we will do on the first day of every treatment is we will attach

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radiation detectors to different locations of the patient's body and to make sure that the radiation beam is exactly as we expected and if we see small variations then we can make changes to the treatment plan but generally it is an extra safety level that we can employ and convince ourselves that everything is working correctly.

Chagpar Tell us a little bit more about how radiation actually kills off cancer. Is there any interesting new research that is going on in terms of that, because it seems like we always have a bunch of ways to kill cancer, surgery, chemotherapy, but how exactly does radiation work and how are you advancing the fields in terms of that?

Carlson Most cancer patients get a combined modality treatment as the big picture and about just over half of our cancer patient's receive radiation as part of their total treatment. So I am trained as a medical physicist. My clinical practice is in Medical Physics but I actually have a research interest in Biology as well. So what radiation is actually doing, when we have an x-ray or gamma ray that is interacting in the tissue, what is happening is it is generating a secondary electron and that electron is then going on to deposit its dose as it moves through the tissue and when it is doing that it is doing two things, it is creating direct damage so that it is potentially directly ionizing DNA and creating DNA damage or it can produce what we call free radicals and these free radicals can then diffuse to the DNA and interact and also cause DNA damage. So what is actually happening when radiation is interacting with tissues and cells, we are getting a whole spectrum of types of DNA damage. So we have single strand breaks, base damages and there are also double strand breaks. Double stand breaks are believed to be the most critical lesion that leads to radiation induced cell death, so as a classically trained physicist and medical physicist who has been doing some research in the biology area, what my main focus is, can we mathematically describe this process of radiation induced DNA damage and how does that relate to the cell death and to other clinical endpoints that we care about like local tumor control and normal tissue complications.

Chagpar Tell us more about how that works, is it possible to look at double strand breaks in one particular area or are there factors that go into how effective radiation is and these free radicals, do they go all over your body and kill cells even outside of the radiation dose, how does all of that work?

Carlson So the free radical diffusion is quite localized. So that is not a concern. But there are a number of other factors that can affect the formation of DNA damage and cell death and one of those is actually oxygen level, the oxygen concentration in the cells. We know that if we remove oxygen say from the cell population that we can actually reduce the yield of DNA damage and this can be shown in vitro in the laboratory, it can also be looked at clinically so we know now if we have say a tumor that has a lower oxygen concentration and we have quite hydrogenating oxygenation among human tumors and different tumor sites, but generally those with worse levels of oxygen are going to have a poor prognosis and there is clinical data that shows tumor hypoxia is correlated with things like local failure.

Dr. David Carlson is Assistant Professor of Therapeutic Radiology at Yale School of Medicine. We invite you to share your questions and comments with doctors Foss and Chagpar. You can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC and as an additional resource archived programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers right here at WNPR Connecticut's Public Media Source for news and ideas.