Scott Redding: Welcome to The 3Ps of Cancer podcast, where we'll discuss prevention, preparedness, and progress in cancer treatments and research, brought to you by the University of Michigan Rogel Cancer Center. I'm Scott Redding.

Scott Redding: We're here with Michigan medicine radiation oncologist, Dr. Shruti Jolly, to do some myth-busting and to talk about the future of radiation treatment. She is an associate professor and associate chair of community practices in the department of radiation oncology. Her clinical areas focus on lung, gynecologic, and endocrine cancers. She oversees the standardization and quality of care of patients receiving radiation therapy at the numerous University of Michigan radiation oncology community practices across the state of Michigan and also serves as a consultant for the Michigan Radiation Oncology Quality Consortium, focused on quality improvement in patients undergoing radiation therapy for breast cancer, lung cancer, and bone metastasis.

Scott Redding: Welcome, Shruti.

Shruti Jolly: Hi, Scott, nice to be here and to talk to you about radiation today.

Scott Redding: With any treatment option, there are myths, and I know radiation therapy has its share. I have to imagine the biggest one is, is it safe?

Shruti Jolly: That's a good question, Scott. Many patients come in here, wondering about the safety of radiation. Radiation tends to be a scary word. However, radiation has been used successfully to treat patients for more than a hundred years. In that time, many, many advances have been made to ensure that radiation therapy is delivered safely and effectively, and a focus on quality and safety has been a prime thing that we focused on in our department. We have many leaders in quality and safety from physicists to physicians within our department.

Scott Redding: You mentioned physicists and physicians. Are they the same? Are they two different kind of people that work in radiation oncology and radiation therapy?

Shruti Jolly: Radiation oncology is a very multidisciplinary field. We have radiation oncologists, who are MDs, physicians who have gone to medical school, and then have done residency training specific for radiation oncology, and then we also have physicists. Radiation oncologists are the ones who are interacting, usually firsthand, with medical oncologists, surgical oncologists, attending tumor boards, and really figuring out the stage of the cancers and what kind of treatment needs to be delivered. Then the patients come to our department for a full consultation, where we review the indications for radiation therapy, potential risks and benefits, and then a plan is generated to determine how to deliver the radiation treatment safely. The planning process is generally referred to as a simulation. We simulate the patient in the position that they would undergo treatments.

Shruti Jolly: We have radiation therapists, who actually help deliver the treatments day-to-day, and then we have a team of physicists, many of whom have PhD in medical physics, and they help us make sure that the radiation treatment planning process is done safely, and they do quality assurance checks afterwards to ensure the safety of these treatments. Then we have dosimetrists, who actually help us figure out the field arrangements of how the radiation treatments are going to be delivered, how do they get to the tumor, how do we spare the normal tissue around there to best deliver those treatments? It's the physicist who verify that those treatment setup makes sense, what we're seeing on the computer will actually be delivered to the patient. All this is overseen by a radiation oncologist, meaning someone like myself is signing off on this whole process to say that, "Yes, I ensure that the radiation treatment should be delivered in a way that I deem to be safe for this patient."

Scott Redding: What kind of equipment and options are there for radiation therapy? 'Cause it seems like there's a lot of those, as well.

Shruti Jolly: Yeah. Radiation treatment equipment is very vast, and you do hear lots of terminology to describe them, but overall, radiation therapy is broken down into two subcategories, either external beam radiation treatments where the patient lays on the table and the machine goes around them, delivers very sophisticated, generally treatments that are focused just on the tumor, and then there's internal radiation, which is referred to as brachytherapy. This is focused mostly for either prostate cancer or gynecologic cancers. During brachytherapy, radioactive seeds or pellets are implanted close to or within the tumor site. This can either be done during an open surgical operation or outside in a surgical suite. We have a brachytherapy suite in our department that we can do that in, using needles, catheters, or tubes. I treat gynecologic cancers, and we do use these internal radiation treatments for that.

Shruti Jolly: Furthermore, for external radiation, which is likely what is thought of more as radiation treatments where, again, the patient is laying on the table and the machine is going around, delivering these treatments. That's done using high energy X-rays, mostly photons. Sometimes, we also use electrons, but these are targeted towards the patient in a very, as I said, sophisticated fashion to avoid normal tissues. There have been many advances that have revolutionized the way external beam radiation treatments are delivered. X-ray therapy has greatly improved in the last few decades. In the '70s and '80s, we used to use cobalt machines, and that was very low energy X-rays, so the skin dose and skin side effects were much higher. Today, radiation oncologists use high energy, megavoltage X-rays that can penetrate more deeply and minimize irradiation to the skin.

Shruti Jolly: In addition, we have, what we call, multileaf collimators, which allow radiation therapy to provide, what we call, intensity modulated radiation therapy, IMRT. They're, essentially, little leaflets that sort of go in and out during the beam when the radiation treatments are being delivered, and they modulate the fluence pattern of the beam. IMRT is a very sophisticated type of X-ray

treatment, so which instead of relying on just a few static beams to deliver radiation, multiply active modulated beams are utilized. In IMRT, each of the beams is actively modulated during treatment.

Shruti Jolly: Another terminology that may be heard is something called SBRT, which is stereotactic body radiation therapy. This is something that really has, over the last decade, come to prominence where you can give high doses of radiation to a small area and avoid normal tissues. It first started in brain tumors, so radial surgeries. You may hear of a CyberKnife or a Gamma Knife unit, and that's stereotactic radiosurgery because a brain doesn't move once you kind of get it clasped into a mask. You can really give very focused high energy radiation treatments right to that area. Initially, it was limited just to the brain, but over the last 10 to 15 years, we've developed ways to take into account motion in other parts of the body, so we can give stereotactic light treatment, called SBRT, sometimes also referred to as SABR, S-A-B-R, and these are, again, high doses of radiation, given through external beam radiation techniques right to the tumor.

Scott Redding: When we talk about some of the equipment being used, Gamma Knife, CyberKnife, what is the difference? I mean, they both have "knife" in their name, but what is the difference? And are those kind of the gold standard? Are there other type of machines that are available for radiation therapy?

Shruti Jolly: Great question. Gamma Knife and CyberKnife are just trade names for different radiation equipment. The radiation that they're delivering is the stereotactic. Gamma Knife is generally focused on the brain, and CyberKnife has brain capabilities, as well as other body parts that it can radiate. But ultimately, the radiation treatments are generally delivered via, what we call, a linear accelerated. There are many brands of linear accelerators. Contemporary radiation techniques have distinct toxicity profiles. High doses of radiation employ during stereotactic radiotherapy has been associated with obliteration or obstruction of some tubular structure, such as bronchi or bile ducts, and limiting its use in other tissues.

Shruti Jolly: Stereotactic radiosurgery, be it delivered by a linear accelerator or a Gamma Knife, has primarily been used as an alternative to surgery for the treatment of intracranial lesions, such as brain metastasis, arteriovenous malformations, acoustic neuromas, trigeminal neuralgia, and meningiomas. The brain is the ideal location for this approach because there's essentially no internal organ movement, like I mentioned earlier. The Gamma Knife stereotactic radiosurgery system involves attaching a positioning device. You have a frame directed to the patient, and it's done in this treatment unit. Usually, a neurosurgeon is involved in helping set that up and outlining the tumor.

Shruti Jolly: The linear accelerator that we use in our department for brain treatments actually is frameless, so it's more comfortable for the patient. It still has a very precise delivery of radiation treatments, but there's been enough advancements in this arena that a fixed frame is no longer necessary. Outside the brain, stereotactic body radiation also replies on patient immobilization

equipment. When we are doing that simulation, the planning process, we do use the immobilization devices for that, for accurate targeting of tumors. The CyberKnife is a linear accelerator, which is mounted on a robotic arm that provides hundreds of beam orientations, and it has been used to treat tumors in the lung, liver, spine, kidney, prostate, and pancreas. We have stereotactic body radiation therapy techniques that really can be used anywhere in the body. We have something called the true beam.

Shruti Jolly: Again, I wouldn't get so fixated on what these machines are actually called. It's more important of what they're capable of doing. When these are being commercialized, it's hard to know what's one versus another, but ultimately, it's the tools that a radiation oncologist needs to use in order to deliver the radiation, so kind of like a surgeon has multiple tools that they're using in the operating room. These are the tools that we have to accurately deliver the radiation.

Shruti Jolly: Furthermore, in our department, we have an MRI simulator. When we do the simulation, CAT scan is sort of standard practice. There are a few institutions that have MRI simulation capabilities. We are one of them. There are certain organs that are just imaged better on MRI. For example, brain, and liver, and pelvic structures. With our MRI simulator, we have the ability to more accurately define those areas so we can focus our radiation treatments accurately to that.

Shruti Jolly: Once we have a really sophisticated radiation plan, and regardless of which equipment we're gonna actually deliver it with, another important aspect of the technology is, how is the radiation treatment actually being delivered day-to-day? Because radiation treatments can be, sometimes, many weeks-long, Monday through Friday, and with stereotactic, they're usually a few fractions, anywhere from one to five treatments is standard for stereotactic types of treatments. To make sure that the setup is perfect every single time is essential.

Shruti Jolly: We use image-guided radiation therapy, which is referred to as IGRT, image-guided radiation therapy, and it utilizes enhancements or attachments, in addition to the delivery component of radiation. For example, we use a cone beam CT scan during treatment to verify that the radiation treatments are going exactly where they need to go.

Scott Redding: Over time, as all these different equipments, the CT scans, has that made it that you can be more focused on actually getting the tumor and radiating just that area, compared to maybe radiating more of the body, like maybe in the past might've been?

Shruti Jolly: Yes, absolutely. I mean, our ability, for example, to treat a tumor that's adjacent to the spinal cord, or the optic nerve, or an area that we're really trying to spare the normal tissue, which is adjacent to ... The tumor is pushing on something that ... Obviously, the spinal cord is a classic example. We can use these stereotactic type techniques to really stay off those areas.

Shruti Jolly: Another area that's gotten a lot of press lately is proton therapy. Proton therapy dosimetrically may have some advantages over photons, but it is a very expensive way of delivering treatments, and clinically, aside from a few handful of situations, mostly in the pediatric world, the clinical benefit of proton therapy over standard photon linear accelerators, a lot of the things that I've mentioned, has really not been found. On paper, bottom line is, protons seem to look better, but in actual delivery in clinical care, other than, as I said, a couple clinical areas where there may be a benefit really hasn't shown a benefit to, frankly, to be able to outweigh the financial toxicity of proton therapy.

Scott Redding: Speaking of clinical areas, are all cancer types viable for radiation therapy?

Shruti Jolly: Most cancers can be treated with radiation. Based on the tumor biology, there are different sensitivities of radiation to the tumor. For example, certain tumors are very sensitive to radiation. Lymphoma is sort of the classic example that melts away with radiation, generally, and then you have more radioresistant tumors, like melanoma and kidney cancers. However, now that we're using stereotactic techniques where we can give very high doses of radiation, we're seeing responses, even in those classically radioresistant tumors. We're seeing them respond. We do see quite a few referrals for stereotactic radiation for the kidney cancers and the melanoma type patients.

Scott Redding: You hear, with many cancers, that some patients get surgery. Some patients just get chemotherapy, or they get a combo of chemotherapy and surgery. Does radiation therapy also join as part of that as maybe a whole slew of treatment options for a patient where they might get all three, or maybe surgery and radiation, or chemo and radiation? How does that all work together when it relates to other treatment options for a cancer patient?

Shruti Jolly: It really depends, cancer by cancer, what type of regimen is ideal. It depends on the biology of the tumor, the stage of the tumor, but in general, surgery is local therapy, so you remove the tumor, and then chemotherapy and radiation treatments can be used as, what we consider, adjuvant treatments, meaning that to kind of help prevent the cancer from coming back. Chemotherapy is used as ... It's IV infusion. It gets all over the body. So, if there's already microscopic disease elsewhere, it can get at that in a curative setting, and then radiation treatments locally, so in maybe the post-operative bed, so where the tumor used to be. If that area needs some sterilization because they had positive margins or there's a worry that there may be microscopic disease left behind, or we know from previous data, for example, in breast cancer, you do a lumpectomy, but the recommendation is to then go back and treat the entire breast with radiation to prevent local recurrences, which eventually translate into a survival benefit if you can prevent that local recurrence from happening. That's one way of integrating surgery, radiation, and chemo.

Shruti Jolly: There are certain cancers that are not considered resectable, so they're not good for surgery. Either they're too big or they're in a location where getting it out in its entirety is not possible. Then, radiation treatments can be used as first

line local therapy, with or without chemotherapy. Sometimes we add radiation and chemo together because chemotherapy, not only does it help with the systemic control, but can help as a radiation sensitizer, meaning help radiation treatments work better.

Shruti Jolly: For lung cancer, for example, for gynecologic cancers, we do concurrent chemotherapy and radiation. Patient may have radiation treatments Monday through Friday every day for multiple weeks, and chemotherapy is also going on during that time once a week. So, say for example, every Monday, a patient goes, gets their chemotherapy infusions, then they come to our department, get radiation, and then Tuesday through Friday, they get just radiation, alone. The idea is to help shrink the tumor, and many times, it's curative to do it that way. Occasionally, we'll use chemotherapy and radiation treatments together to help shrink the tumor so surgery can be feasible afterwards. That is referred to as neoadjuvant treatments where you give it up front, either chemo, alone, or chemo plus radiation, and then we do scans again. Based on how the tumor has shrunk, then we ask the surgeon, "Is it now possible to do a surgical resection?" There's multiple ways to use chemotherapy, radiation, and surgery.

Scott Redding: One of the key buzzwords right now out there in the medical field is immunotherapy. Is there immunotherapy and radiation, any kind of combos of that? We talked about it from a surgical and chemo, but as we start to look at some of these newer treatment options for patients, how does that all tie together?

Shruti Jolly: Yeah, there's definitely been a lot of press and interest, and rightfully so, for immunotherapy. Immunotherapy has been a mainstay in melanoma for a long time, and more and more, other cancer types are finding out that you can use ... Immunotherapy are a class of drugs that are used to take advantage of the patient's own immune system to help fight the cancer. While it is medical oncologists who deliver chemotherapy are also in charge of immunotherapy, there's lots of things, in conjunction with radiation, that we're learning. For example, radiation also stimulates the immune system. So if you give immunotherapy, in combination with radiation treatments, you may be able to get a synergistic effect of the immune response that could translate into long-term increased survival.

Shruti Jolly: A lot of this is still being understood, so there's a lot of lab work being done, and then translational work to try to get this into the clinic. There are multiple, multiple clinical trials that are ongoing with the using immunotherapy, immunotherapy with various chemotherapies, immunotherapy with surgery, immunotherapy with radiation. Specifically in lung cancer, this is a very hot topic. There was a study that just came out about 12 to 18 months ago that showed in stage three lung cancer patients who are not considered to be receptacle, so these were patients we were treating with chemotherapy and radiation, adding an immunotherapy drug after chemoradiation improves survival. This was the biggest breakthrough we've seen in lung cancer for a long time. There's lots of investment in research in this arena, and I think that's

probably going to be the biggest thing that's gonna happen with cancer therapy as these trials continue to evolve in seeing improvements in cure rates.

Scott Redding: Are there other areas where clinical trials are showing benefit outside of just with immunotherapy combined?

Shruti Jolly: There are various aspects. I mean, targeted therapy, that's another very interesting area where you can find the actual mutation that is leading to a certain cancer and being able to target that mutation. In our department, alone, we have at least 30 ongoing clinical trials that are focused on radiation-specific questions. A major focus of our department has been ways to individualize radiation treatments. We've looked at it for liver cancers, lung cancers, head and neck cancers, brain tumors, where instead of using the same radiation dose and same chemotherapy and same everything for every patient that walks through the door with a certain cancer, are there ways that we can know something specific about the patient's biology to know, how are the normal tissues of this specific patient going to respond? How is the tumor in this patient going to respond? Using blood biomarkers upfront, mid-treatment, to help us individualize that patient's radiation treatment.

Shruti Jolly: That's been a focus of our department for decades, and so not only using blood biomarkers, but radiographic imaging to see early changes in tumor or normal tissue, such that we know that this specific patient is less likely to have side effects from radiation, that we do have the opportunity to increase the dose of radiation in a certain patient, versus another patient who may have tendencies to have more likely to have either acute or long-term side effects, and in that patient, perhaps reducing the dose or bringing in another chemotherapy agent or immunotherapy agent to help intensify the dose in a different manner. That is for radiation. That's what we're focused on learning and really personalizing treatment for patients.

Scott Redding: Have you seen any improvements with patients as you've looked at those?

Shruti Jolly: I can speak of lung cancer because that's one of my clinical and research focuses. We are seeing that patients with lung cancer, we do a mid-treatment PET scan, and we are obtaining lots of different biomarkers. There are inflammatory biomarkers, which we call cytokines, or specific DNA biomarkers are trying to understand which patients are likely to benefit from immunotherapy. Even though immunotherapy is finding lots of great benefits, it's not effective in everyone, and there are side effects associated with immunotherapy, and so that is what we're looking at, and we are finding that in certain patients, based on a specific biomarker, we can improve the dose for the tumor.

Shruti Jolly: The other thing we're focused on is looking at heart and lung function in lung cancer, specifically, that we want to give the highest dose possible, but we don't want to cause heart and lung damage. So, we've been involved in looking at various cardiac factors to help reduce that, and we are seeing some

improvements in the way patients are going through these treatments based on that.

Scott Redding: You just mentioned the side effects with immunotherapy. For radiation therapy in general, are there side effects? What are the side effects? I know some of the other treatments, between chemo or surgery, that there's all these different kind of side effects people need to be worried about.

Shruti Jolly: Yeah. Radiation treatments do, in fact, of course, have side effects. The common thing that's sort of across the board that we warn patients of are fatigue, that you may feel more tired during treatments. Generally, radiation treatments, unless we're treating a very large field, don't affect blood counts, like chemotherapy does, but there is some insult to the body, and therefore, patients tend to feel a little bit more tired, but the remaining side effects from radiation are really dependent on which body part the radiation treatments are being delivered to.

Shruti Jolly: If you're, for example, treating the head and neck area, you may have throat irritation and swallowing issues. Usually, these tend to be limited in scope and time, and we have medications to help patients through these acute side effects. For example, in breast cancer, many times, we're trying to treat the skin, so therefore, you see skin side effects. For lung cancer, as I mentioned, heart and lung side effects. If we're treating close to the bowel, there can be bowel irritation, so really, very specific to where we're treating. Then long-term side effects are mostly related to scarring and fibrosis, and this is also very much dependent on where the radiation treatments were delivered.

Scott Redding: Well, Shruti, thank you, again, for the time today. What I usually like to do here is ask if there's a takeaway that our listeners would get from this. What would that be from you?

Shruti Jolly: Radiation treatments are complex. There's a lot that goes on with the delivery of radiation treatments. I think important things to note are as our cell phone technology has improved substantially, so has radiation technology, our ability to give radiation treatments in a very focused way has really improved substantially, but when we are dealing with high doses of radiation and trying to avoid very sensitive tissues around there, being in a center that one does a lot of these types of treatments and having the quality and safety measures in place to deliver these effectively is very important. Having a team of doctors taking care of your cancer, this is a very multidisciplinary field within the department of radiation oncology, like we mentioned, as well as outside. There's lots of players involved. We are, of course, always trying to improve upon that here in our department.

Shruti Jolly: Thank you so much for having me, and I really enjoyed telling you about all that's going on in our department.

Scott Redding: Thank you, again.

Shruti Jolly: Thanks.

Scott Redding: Thank you for listening, and tell us what you think of this podcast by rating and reviewing us. If you have suggestions for additional topics, you can send them to cancercenter@med.umich.edu or message us on Twitter @UMRogelCancer. You can continue to explore The 3Ps of Cancer by visiting RogelCancerCenter.org.