Hello friends and colleagues and welcome to episode 159 of Dermasphere, the podcast by dermatologists, for dermatologists, and for the dermatologically curious. I'm one of your hosts, my name is Luke Johnson. I'm a pediatric dermatologist and general dermatologist with the University of Utah. And joining me, of course, is... This is Michelle Tarbox. I'm an associate professor and chair of dermatology and dermatopathology at Texas Tech University Health Sciences Center in beautiful sunny Lubbock, Texas. We've also got the pimping bell. [Pimping bell] Two of them, one for Michelle and one for me. The pimping bells exist to highlight especially question-worthy content, so pay attention when the pimping bell rings, especially if you are an academics, either as a learner or as a... ...learney. [Laughter] And we've got a special guest today, so we are very lucky to have on Dr. Jake Scott. Jake, thank you so much for joining us. It's a real pleasure. I'm excited to be here. Thanks. Excited to have you. We're going to talk radiation for skin cancers today. Do you want to start just by giving us a little bit of an introduction to yourself and how you know about this stuff? Sure. Happy to. First of all, thanks for having me on. This is great. I feel I'm honored to talk to dermatologists about this because I'm actually a radonk. And so I'll tell you my brief story and then we can dive right in. I was originally a physicist in college at the Naval Academy and went on to do nuclear engineering on a sub, and weapons and engineering and all those things as a 20-something-year-old make a ton of sense. But when I finished, I realized that I could also use my knowledge of the atom for good. And so I went back to med school as a little bit of a late bloomer and fell in love with radiation oncology and oncology in general and went on to a radiation oncology residency at Moffitt Cancer Center. Halfway through that, I started realizing that standard of care is great and it's amazing to learn how to do that in the best way possible and take care of folks, but also that sometimes, especially in oncology, we need to try to do better. So I took a break from residency to do a PhD in applied math in England at the University of Oxford and came back from that, really recharged and dove into the rest of my residency and then took a job here at Cleveland Clinic where I'm a staff physician scientist doing mostly research. And the research I focus on is novel therapies in oncology. And then, of course, I do practice radiation oncology as well. But I think the reason I got into this space is because of the new technologies that exist. And I think that there was an interest to consolidate the research and really try to do a better job understanding the benefits, lack of or benefits of image guidance in superficial radiation therapy, which everyone on this call knows is a specialty that the dermatologists have been using for longer than radiation oncology has existed. And so just being pulled in to kind of try to help to understand how image guidance does or doesn't help with outcomes and what that looks like in the dermatology office was the ask. And after I started diving into the research, I kind of

became a believer after seeing the data. And so we formed a nonprofit society called the Dermatology Association for Radiation Therapy, which is an academic nonprofit society to really consolidate the research and educate folks on the benefits of this new technology. And so that's why I'm here. I think that's the hat I'm wearing today. But you can see I've put on and taken off a lot of other hats in my life. For sure. And there's a journal article that might help guide our discussion. It looks like it was from the Dermatology Association of Radiation Therapy or DART. Apparently, this is published in the journal Skin, and it was "Image guided superficial radiation therapy is safe and effective and a first line treatment option in selected cases of non-melanoma skin cancer." So I remember learning that radiation could be used as a treatment for some skin cancers, our squamous cell and basal cell carcinomas. When I was in residency, usually we felt like if people were quite frail and not good surgical candidates, but you still wanted the cancer gone, then you could use this radiation thing. But I don't think I ever saw it happen. I don't even know if I was ever at an institution where they had the devices available. So I assume this image guided thing is even more advanced than what I potentially learned about in residency. Can you give us sort of an overview of just radiation for skin cancer in general? Yeah, absolutely. So like I said, radiation for skin cancer is older than radiation for any other cancers, because before we invented the high energy mega electron volt machines that we use as radoncs in our clinics, you know, these big linear accelerators, before we had those, we had little x-ray tubes, which would create mega electron volt, so like, excuse me, would create kilo electron volt electrons, photons, excuse me, around 50 or 100 KeV. And those have been in use forever, mostly by terms for superficial cancers, for superficial skin cancers. That's still in use. But really, the way the history goes is really interesting. And, you know, I was a terrible historian in high school and then just chose physics. But I do think it's interesting here to think. So you started with, I'm going to call it SRT or blind SRT, which is what we use for 100, what you guys have been using for 100 years. And the outcomes are pretty good, you know, 80, 85 percent local control. And before the invention of MOHS, if you have sort of a blind excision, if we want to use that same terminology, that's kind of around the same place. Right. Problem is, it takes more treatments with radiation. If you can just cut it out, go for it. It was about the same, mid-80s, pre-MOHS, right, pre-MOHS. And so those were kind of like equal options. And it's like, like you said, Luke, it's like if it's a patient's not a great surgical candidate or they live far away, why not just cut it out? But if you have a super producer of keloids or bad diabetic or any number of other things that would make surgery hard, you could use this other option in the form of superficial radiation. Enter MOHS and all of a sudden the outcomes got way better for surgical excision. You know, you went from mid-80s to mid to high 90s with

MOHS micrographic surgery. And so all of a sudden, really, this SRT started falling out of favor because now you're offering a second line therapy, or sorry, now you're offering an alternative therapy that's got a worse oncologic outcome. And so even if the patient's frail, even if they're a bad surgical candidate, the tides shifted as they should, right, because as we physicians know, there's always this risk benefit stuff and talking to your patient about it. So you don't say, hey, do you want 10% more chance this recurs or a risk of bleeding or whatever? And usually that just went to MOHS and that really became the standard of care, as everybody on this call probably knows. In parallel, and so SRT still exists, the blind superficial radiation therapy still exists, it's still paid for. People still use it in some cases, but it's fallen out of favor for the most part. Now, in parallel, in my field, in radiation oncology, something else happened. And so over the course of the last few decades, we've moved from, again, we use these much higher energy deep seated tumor treatments called mega electron volt, which is just the same photons, just a thousand times more energetic. And we treat deep seated tumors and also sometimes skin cancers, as people know, more locally advanced if there's lymph nodes, stuff like that. And that still is a totally reasonable therapy. But you have to go into a cancer center. It's a whole kettle of fish. But in our field, what we did was we realized about 15 or 20 years ago that if we started imaging every day, so we started taking a daily cone beam CT, our outcomes started getting better. Not super surprising. You see the tumor, you need to move the fields around a little bit, you do better. So when I first started training, we took an x-ray once a week, make sure everything was kind of in the same place and went forward and just checked. Nowadays, it's very standard that we take a miniature CT scan every single day, line up to the tumor. Maybe the tumor has even shrunk or gotten bigger. We can change our fields. Maybe the tumor has moved or the normal anatomy shifted. We can shift the fields around. So we've moved from radiation therapy to image guided or I.G.R.T. And that's really what the following that historical trend in radiation oncology is what happened with the makers of some devices that now allow image guidance in the form of high resolution dermal ultrasounds, which I think a lot of your users might know about or listeners might know about for other purposes. And they added that into this superficial radiation therapy. So now you have following the history of radonc, you kind of have an evolution of technology for derms. And this new device came out in 2016, I think, where you could now directly image as often as you want a skin cancer and then treat it with this radiation field. So some folks would be like, why do you need to visualize it? You can see it. So the same reasons you need to visualize the margins and most is the same reasons you want to visualize the margins here. You can have a smaller, more precise field. You radiate less normal tissue. You know, radiation does carry toxicity, so you

don't want to do too much of it. Same with the surgery, right? You could always you can you can get 100 percent local local recurrence. No, not rates. You can get 100 percent local control rates if you take off enough of a margin around a skin cancer. But you want to do most to take off less. So the same thing exists here. There's this desire to say, hey, what does the edges look like? And this high resolution ultrasound tells you where the edges are. Also, what's the depth? How high energy do I have to turn this thing up to? Can I turn it down or has it swollen? Because sometimes radiation causes lymphocyte infiltration. So I need to get more. So really, you're able to just kind of just check and look every day. And so that was what came into into being in 2016. And it's really taken off. And so there's I think, you know, there's hundreds and hundreds of users of this now as in dermatologic space in Durham offices. So patients can get treated right where you guys are, where you diagnose, where you'd normally do it. And what the question was, was does the imaging help? And so the research that we've been doing and our society has been putting forward, like you suggested, Luke, and the article that you put down is a nice review. But there's a series of articles in 2024 and 2023 that really look at kind of all aspects of the outcomes of this new technology. And they're a large series, 20,000 something patients, five year follow up. And it looks like sort of not surprisingly thinking about the history, but it looks like we've taken what that blind SRT data looked like, which used to look like the blind excision data. And if you add the imaging of Mo's, you get about 10 percent more benefit and adding the imaging in the form of this high resolution ultrasound seems to do the same thing. And so it's pretty neat now as it looks like from all our data, of course, no one's done a head to head between Mo's and this. But I don't think it probably ever will happen just because of the way that technology evolves. But it looks like we have two options that are now have equipoise when it comes to oncologic outcomes. And so what's nice about that is you can go back to looking at the patient and talking about pros and cons and not saying, hey, do you want to do you want to avoid a surgery and do this radiation thing? But it's but it's not going to do as good. You can go back and say, hey, here are the two options. What makes more sense? And it can be in the same Derm office. So you're also not sending your patient out elsewhere, farther away from their home like that. So I think what we have now in the opinion of our society and I think the literature supports is sort of three equal treatments. You can do Mo's excision. You can do an image guide to radiation or you could also do radiation in a cancer center with RAD-ONC. But I think for a lot of the very early lesions, that's probably a little overkill because it can usually be handled easily in the Derm's office. And so I think that's great because what we all want is to give our patients the best treatment for them. And we don't want to give up on outcomes. So if you have three treatments, they all work great and it really becomes a

choice and a discussion between you and your patient about what's best for their life, what's best for their overall outcomes, both toxicity, morbidity and also cancer outcomes. And so I think that's a probably long winded answer to a short question, but I hope it gave some color. For sure. So my impression is that the finances are a big part of some of these decisions. So we've all got scalpels in our clinics and a lot of us have access to Mo's surgeons and I don't know how many of us have access to what I presume are extremely expensive radiation devices. And then I also wonder if there's a tension if you have a device, are you more likely to recommend it to people who wouldn't necessarily be first line candidates for it? Can you talk a little bit about that issue or those? Yeah, those are those are all good questions. And you're you're bang on right about it. I think I've talked to a lot of users, I'd say folks who have these devices in their offices, who are also most surgeons. So we have probably a couple of hundred American College of Most Surgeons folks out there who have these devices. There's a couple of hundred American Society of Most Surgeons folks out there who have these devices. And then there's actually also a number of medical germs, not nonsurgical germs who also have these devices. And so I think that you're certainly right in that having a new option can if you didn't have it, you couldn't recommend it. But when I've talked to the most surgeons in particular, let me focus on those folks, because I think that they're used to mostly using most micrographic surgery and giving their patients great outcomes. When I talk to those folks, having one of these devices as an option has really allowed them to kind of triage the surgeries that are like to basically take patients who they know would have an incredibly complex most surgery and they know would have a difficult reconstruction and they know might have functional or cosmetic issues and triage them to the device. And what it does is it actually does a couple of things. One, the cosmetic outcomes on a face or the functional outcomes near a mouth or as you all know better than I do, the tip of the nose, tip of the ear. It's hard to cut those off and not have changes in your cosmesis. It's hard to cut off part of the lip and not have changes in function. So triaging patients with those issues in particular to the machine, to this radiation based treatment can really help your practice because it kind of turns down the risk and allows you. It sort of seems counterintuitive, but actually a lot of those folks are now able to do more most procedures because they're having more less complex ones and so taking the more complex ones and that would have bad outcomes and moving them toward the machine. So I think that instead of encouraging the use of something that wouldn't have been used before, it's more about making a great choice for the patient in front of you. And I think most folks I talk to book out and again, I'm not a derms here, but I've talked to folks who say, you know, I'm looking out three, four months for my most surgeries. And what's happening is that I think those

folks are able to kind of decompress that most schedule, get through more patients, cure more patients, give more access and have another set of patients who are being treated in a different way. And so I think that was the second question you asked. And of course, I think that the billing rates, if you want to think about collections and things like that, I think are pretty similar lesion for lesion. They're on the same scale. So it's not like if you put a patient on radiation, you're going to get paid triple or if you put a patient on Mo's, you're going to get paid triple. So there's not really, I don't think, a ton of financial incentive difference. Not that any of us took an oath to that part of medicine, but it is real. I get it. When it comes to the finances of the machine itself, you're right. They're not cheap. You know, they are definitely more than a microscope and a scalpel. There's a bunch of solutions out there, different companies that kind of help out with management of that. Because the other issue is that you need a radiation therapist to help deliver it or you ought to have a radiation therapist to help deliver it. You need a special room with shielding. There's certainly some logistic issues, but there are some ways for docs, private practice docs, anywhere, big cities, not big cities, to sort of get around those logistic issues with the help of partner institutions. And I think that my nonprofit society certainly is sponsored by several of those, but I think we should maybe leave that discussion for a different day. I was going to ask if it required special training, but it sounds like there are radiation therapists who get that training and are part of your clinic as well? Yeah, that's right. So by law, depending on the state, you don't necessarily have to have a radiation therapist. As our association, DART, has published a bunch of appropriate use guidelines that have been co-signed by many, many, many docs. And I think that what we're moving toward is all the research that's been done that shows, again, not head to head, but shows equipoise between MOHS and this new technology. All that's been done under the rubric of appropriate medical physics support delivered by a trained and licensed radiation therapist. And under the supervision of a larger group that we have availability for complex cases and recommendations from a sort of larger conglomerate, almost like a cancer center, like I'm not going to say supervisory, but consultant role that's available to the DERM. Because I think certainly, you know, dermatology residencies do include superficial radiation, but this is new technology. Just like people who were trained as DERMs before MOHS existed, you can go get trained to do that, of course, because that's how new technology works. I think the same exists here. There's opportunities. I know the American Society of MOHS Surgery is offering an educational course around this at their annual meeting. I'm sure it's going to start penetrating the other societies as well in the meantime. But I do think our society promotes or advocates for a licensed radiation therapist to be part of the treatment. Again, that's not, I don't think a legal requirement everywhere, but it is, I

think, recommended. It also removes a lot of the burden from the DERM's office, right? Because, like you said, if this isn't something you train with, you know, you don't want to give suboptimal care. And even, you know, as a radonc, every single one of my treatments is delivered by a radiation therapist, right? It's sort of part of the part of the world. In 2025, these are complex devices. I think, you know, in 1975, the device was a little simpler to use and we'd often have, you know, med techs or LPNs or nurses operating them. But I think nowadays, especially with the intricacies of image guidance, I think having someone who's trained and board certified and licensed is important. Will you remind me and our listeners what are the side effects or toxicity associated with radiation treatment? Yeah, for sure. So everything we do in medicine has an up and a down. You know, I think the toxicities of deep-seated radiation therapy, or what I do for the most part, are very different than superficial radiation. So superficial radiation doesn't penetrate very far into the body, which is great, which is why it's called superficial. But the side effects, you know, they're real. You can have inflammation in the area around it. In the very worst cases, you can have, you know, burning of the skin and you can have it can open up. So there's actually a specific toxicity criterion system used for that called the Radiation Therapy Oncology Group Classification, or TOG. It's one of our old cooperative groups. And it goes from zero to four, zero, nothing, four, proper ulceration, requiring treatment break, things like that. With these novel, with this newer superficial radiation and the sort of fractionation schedules we recommend, which that just means how often you treat sort of something like every other day, the toxicities are really pretty minimal. So my mom actually just had this treatment a few months ago on her chin, and she definitely had some redness and some itching, but it never opened up. There was no issues. And within about seven to ten days, those were gone. But like you said, there are real toxicities like anything we do. I imagine that most people listening here say, hey, most of the time I do mows, there's a small scar, it goes away, no one cares. But every once in a great while, bad stuff happens. Very same thing here, right? For the most part, patients come and go, don't even, aren't even bothered. You know, are you turning the machine on, doc, kind of questions. And then, but in the very rare scenarios, you can certainly have patients who are more radiation sensitive than their normal tissues are more radiation sensitive. You can have ulceration. You know, for the most part, I'd say like. Then we can look the numbers up together, but I'd say 10 or 15 percent of patients have redness and itching and one to two percent have anything much more significant. And, you know, it's interesting. The one thing we always skip over is this secondary malignancy risk. You know, any chemo or radiation therapy, both are DNA damaging agents. That's what they do. And so they come with secondary cancer risks. There actually haven't been reported secondary cancers from superficial

radiation ever. That said, they probably have happened, you know, in deep seated radiation therapy, which I do. You know, the risk is something like one in two thousand. And that's from really long term breast cancer research follow up. So most common cancer in the world, breast cancer, women live a long, long, long time afterwards and they're getting much more tissue done, radiated at a higher dose. And those women have something like one in two thousand chance of a sarcoma arising in the radiation field. And that's well documented. It's usually 15 years out. And so if you extrapolate that back to superficial, it makes sense that there would be some risk. But I think when it comes to the risk is sort of scaled by volume of tissue radiated. So if you have an entire breast and chest wall compared to, you know, a few millimeters of skin, you're already at several thousand times less risk. And then and again, the sort of lead time is something like 15 to 20 years for those secondary malignancies. So I think while it's probably possible, it's not something we've ever seen. And I think in especially the elderly population, not something that would you'd worry about. It would also be only in the area treated. And for the listeners who are studying for their boards, what is it that characterizes poster radiation angiosarcoma of the breast? It is NIC amplification. So NYC amplification is the test question for that. I want to pick your brain about something. So I do utilize adjuvant radiation for some patients. We've also directed some patients for therapeutic radiation. And one of the challenges we've run into is the shin. So radiation for perineural invasion of squamous carcinoma on the shin, because boy, those wounds don't like to stay healed. Do you all have any like management pearls or anything like that from the radiation oncology side of things? Great question. So are you talking in particular about patients who had surgery and then a post-op radiation? Yes, post-op radiation for perineural invasion on the shin. So closed initially, had to do the radiation therapy and then just chronic ulceration on the shin. Yeah. So lower extremities, always tough. Thin skin, poor vasculature, hardly anything underneath it to support it. I mean, this is like this is the setup, right? The setup for badness. And so, you know, one thing I'd say is maybe that would be a great patient for only radiation if you could sort of triage that in that direction. But if you're in the situation where you've already planned your surgery, done it, there's perineural invasion, darn it. Let's do something adjuvant to make sure the cancer doesn't come back. And now you have a non-healing wound. First of all, it's a bummer. And I know all the sort of normal things. And in Radon, these things do happen too, right? And I think we do all the things you do, pack the wound. We do often use hyperbaric oxygen. I don't know if that's something that's commonly done in dermatology, but certainly that does help a ton. It's hard to sometimes find it's, you know, logistically challenging for patients because it's often, you know, tens or 20 treatments or more. And it's going and sitting in a room. So I

was actually a diver in the Navy. So for me, hyperbaric oxygen is like what happens when things go really bad. So I always have this terrible idea of what that would look like, having never actually had the bends or had to go to it. But when I send my patients off for hyperbaric, I'm like, no, no, no, don't worry. You're just going to be able to read the newspaper. It's going to be fine. And then I do think, you know, there's a number of newer technologies that are coming to the fore. I'm going to accidentally advertise for a friend of mine's company, but there's a company in Utah that's now doing what's called Polarity TE, where it's really cool. It's originally for burns, but they're able to grow an ellipse of skin, take that and make it do a large now your own skin graft. And so I think, you know, things like that that are coming to the fore using some of these new stem cell stem cell technologies to really, you know, that's a grafting technique rather than a healing technique. But I think that, you know, we're in an exciting world where, you know, our understanding of biology is really just accelerating so rapidly. I'm hopeful that some of these issues of the past will go away. But, you know, those wound healing issues are real, especially when you're combining both surgery and radiation on skin that doesn't like to heal anyway. Yes, that's a very good point. I appreciate your perspective on that. Thank you for sharing. Thank you. Yeah, Jake, thanks for all of this overview. I learned about radiation for the skin and that there are some updates to our technologies and they sound like cool options if you can access them. Are there other things you would like our listeners to know before we let you go? I'd like to just say thanks to everybody out there taking care of folks out in the world. You know, I think that this is a tough profession, medicine in general, and the fact that you're engaging not only maybe on your car ride in to learn some more is awesome. And I think, you know, I feel it's a huge honor to be able to talk to docs from different specialties just because I feel like, you know, we're all one tribe and, you know, we're all we all took an oath to help folks. And there's not a lot of professions like that anymore. So I just want to say thanks everybody for the work they do. And then a shameless plug for society. If you want more info, maybe the podcast website would put our link up there, but it's Durham Association RT dot org or you can just Google Dart or Dermatology Association for radiation therapy. We're welcoming new members. We do have educational materials, appropriate use guidelines, and I think it's a great community of folks. Even if you're just radiation curious, come on over and learn stuff. And if you want to be more involved, there's tons of tons of opportunities for for helping with our research or getting involved in using the therapies yourself. So, yeah, thanks for the time. And it's great to meet you both. Likewise. See you next time. So good to see you. All right. I want to talk about something else from outside our specialty. This is from a journal called the Journal of Plastic Reconstructive and Aesthetic Surgery. And it's about a condition called

Lipidema. Lipidema. It's called Lipidema. What we don't know, the authors include RFD Vanlapara and PH Fosaprez out of Belgium. So a month or two ago, I had an adolescent girl come into my pediatric dermatology clinic and her mother was concerned that the patient had a condition called Lipidema. And I was not familiar with such a thing. And so we had to look into it and the resident who was working with me at the time, Dr. Ali Eisenbeis, thanks for your help, tracked this one down as a pretty decent review. So I guess this Lipidema thing has been described for a while. There are even some diagnostic criteria that were proposed in the 1950s. But my impression is that social media has given Lipidema a new life in the modern age. It has. I've actually seen a patient advocate that was kind of showing her Lipidema and talking about her family history. Do you remember learning about Lipidema in residency, Michelle? I learned about it in dermatopathology fellowship because you see some dilated nictatic lymphatic vessels. Okay, but not in residency. So I can't just blame my particular residency program for not educating me thoroughly on this condition. No shade to your former professor. Go ahead. Not at all. So I guess Lipidema means fat looking uncomfortable legs in women that are not related to other medical conditions such as obesity or lymphedema. There are no obviously great treatments, though it seems liposuction has the best data. According to this article, Lipidema affects 10 to 20 percent of women. Wow, that's that's a high percentage. I know. So I think there's this tangential philosophical discussion of where do we draw the line that something is considered a medical condition versus a variant of normal. Keratosis Pilaris comes to mind. I don't know what percentage of the population is affected by that, but I wouldn't be surprised if it was 10 to 20 or higher. But we tell people it's a variant of normal. There are things you can do about it, but it doesn't have like it's not a disease. It's not a medical condition. And so how does this play into that? That's a very good question. Kp is pretty common about like half at least of adolescents are affected with Kp and up to like 40 percent of adults. So very, very common. But, you know, 10 to 20 percent is still a lot of patients. Sure is. So apparently you can divide up Lipidema in a few ways. So one is its distribution. So there's five different distributions. There is one that is the pelvis, buttocks and hips. And there's another distribution that's the buttocks to the knees. There's buttocks to ankles. And then less commonly, arms and finally, just lower legs without the buttocks and pelvis being involved. But like the foot is never involved, which is supposed to be somewhat distinguishing. So sometimes you can use lymphedema. You can tell the foot will usually swell in lymphedema, but in lipedema, not so much. That's right. And there's apparently three stages of Lipidema. Stage one, stage two and stage three. It's been named very straightforward. And it's basically how severe they get. So in stage one, you have thickening and softening of the subcutis with small

nodules, but the skin is smooth. On stage two, you get larger nodules due to increased fibrous tissue and the skin texture is uneven, which they call the mattress phenomenon. And in stage three, there's thickening and hardening of the subcutis with large nodules, disfiguring lobules of fat on the inner thighs and inner aspects of the knees. And there can be overhanging masses of tissue. And I guess there's like an end stage, stage four, called Lipolymphedema. Okay. Diagnosis is difficult as there are no agreed upon criteria and there is no specific imaging. But some proposed diagnostic criteria include the following. Disproportionate body fat distribution. Bilateral and symmetrical limb enlargement. Doesn't get better if you lose weight. There's pain or tenderness and easy bruising. There's increased sensitivity to touch or limb fatigue. There's minimal or no pitting edema. Your pain and discomfort doesn't get better with limb elevation. And there's not really involvement of the hands or feet like we mentioned. So a lot of that is to try to differentiate this from other similar disorders like potentially obesity. The pathophysiology of Lipoedema is poorly understood, but it is thought to have something to do with fat cells, lymphatics, and drainage. Maybe the stuff you saw into the microscope. So for example, an affected person might have fatty cells that are more prolific or larger than normal and these could crowd out endothelial cells, creating relative hypoxia, which then creates some fibrotic change. The fat cells can also squish the lymphatics, reducing lymphatic drainage. According to these authors, some biopsies and liposuction aspirates also have demonstrated enlarged extracellular matrices. So increased water or edema could also play a role because remember the ECM is where you have all these proteoglycans that hold onto water. There's also a family history in a decent percentage of patients, anywhere from 15 to 73% of them, suggesting perhaps an autosomal dominant inheritance with incomplete penetrance. Onset is usually in adolescence or early adulthood. The differential diagnosis includes a bunch of stuff, like obesity, which is a comorbidity in 38% of patients with Lipoedema. But again, importantly, Lipoedema does not seem to improve with weight loss. Lipohypertrophy, another condition with which I am unfamiliar, seems similar to Lipoedema, though there is no edema and no pain in Lipohypertrophy. So again, where do you draw the line between normal and abnormal? Lymphedema, like you mentioned, most of us know this. You mentioned the foot, so stemmer's sign, they mentioned. You remember stemmer's sign, Michelle? I remember making a mnemonic for myself about it because it affects your stems, I believe. Your stems. What are your stems? Have you never watched Clueless Luke? A long time ago. They talk about stems. So the stems are like one of their slang words for legs. Okay. But I think it has to do with like you pinch the toe or the finger and you're trying to like lift a fold of skin at the base of the toe or finger. So if you can't lift it, then the stems are like edematous, you know, because like your arms

could also be stems. As if. As if. Okay. You got it. I'm proud of you, Luke. Good job. You try to pinch a fold of skin at the base of the second toe. And if you can't, then stemmer's sign is present and that's more likely lymphedema. And lymphedema generally responds decently to compression therapy if patients can't tolerate it, while lipidema does not. Another differential is venous stasis disease. Most of us know what that looks like. Also Durkheim's disease. Ah, Durkheim's disease. Tell us about Durkheim's disease. So I recall this having like sort of symmetric, painful. It's like also called adiposis dolorosa, I believe. Am I correct? Aha. And it's sort of gynecoid distribution of fat, but it's like very tender and it tends to co-associate with like depression and anxiety. What do you mean by gynecoid? I like like hips and buttocks and stuff more than the upper body. But there are some deposits on the upper body too, I think. Yep, that's right. And then there's a condition called benign symmetric lipomatosis. This is another one that is probably buried in the textbook somewhere. It's increased accumulation of fatty tissue with typical disproportion. Generally in the neck, shoulders, arms, or pelvis, there's no pain or edema associated. So those are the things on your differential. I would assume obesity is more common than lipidema, but all of the rest of these seem probably less common if 10 to 20 percent is real. There are some imaging techniques like ultrasound and lymphocintigraphy that are not diagnostic of lipidema, but can help rule out some things on the differential. If you want to treat lipidema, it involves both conservative approaches, what they call conservative decongestive treatment or CDT, and liposuction. So CDT involves massaging the area using compression garments, though they're not especially effective, physical exercise, and addressing comorbid conditions that can worsen lipidema, such as obesity and venous insufficiency. And there are particular versions or techniques with liposuction that are thought to be best, specifically those that don't disrupt lymphatics. So if any of you guys out there do liposuction, I wondered if you call yourselves liposuckers. But if any of you guys out there are liposuckers, you can take a look at this article for some specific recommendations on how to do these techniques for this condition. I really feel that my patient probably just had, like, muscular legs. She was, like, 16, and that's the age when you get muscles and mass, and she was, like, an athlete, I think. So it would make sense to me that she had muscley legs instead of lipidema. I am grateful for her family for inspiring me to learn more about this. It's very cool. I think that any of these conditions that cause those, like, painful skin lesions, especially when there's an associated observable morphologic abnormality or difference, can be challenging. Anything that arises in adolescence is extra hard to deal with, because, you know, I don't know that I would go back to middle school again if somebody, like, paid me, like, the lottery. It would be crazy, because, like, you know, you're just so self-conscious you

think that everyone's looking at you all the time, and that invisible audience thing that people feel when they're in that age group, that's hard to live with. Well, there is lipidema. Have you had patients come in asking about it, Michelle? I actually have had patients with lipidema. So it is something that people get pretty distressed over, not just because of the discomfort, although that's a big part of it, but it's very distressing to women who are really trying to optimize their health and things like that. When they're working very hard, they're exercising, and like you mentioned, weight loss doesn't really seem to budge these very tender, usually pretty dimpled, clinically, fat deposits. So it kind of looks like extreme cellulite, and it's very tender to the touch. One of my patients said that she felt like her legs were bubble-wrapped in this sort of adipose tissue that was very tender and, you know, obtrusive to her personal perception of herself. So I think it can be quite impactful on the patient. It's difficult to manage. There are, you know, certainly therapeutic options, but they don't tend to be covered by insurance, and so those can create an access issue for patients. Very interesting. Well, I'm trying to find a connection between that and our next thing. Let's talk about something that's also sometimes fibrotic and sometimes painful. How about that, Luke? Did I get there? We'll see. We'll see what the listeners say. All right. So I am trying to make a connection now to IgG4-related disease. So IgG4-related disease is a family of systemic fibroinflammatory disorders that are characterized by tumor-affective lesions, story-form fibrosis, and infiltration by IgG4-positive plasma cells. Skin involvement can occur, and so we need to be able to recognize and diagnose these conditions when we see them. So we're going to go over an article from the New England Journal of Medicine entitled "Inibilizumab for the Treatment of IgG4-related Diseases" by authors J.H. Stone and also all the way down to the bottom, we have author E.L. Culver, and there's a lot of authors on this trial, so we thank them all for their contributions. This is relating the results of a Phase III clinical trial looking at inibilizumab in the treatment of IgG4-related diseases and its ability to reduce disease flares in this multi-organ relapsing fibroinflammatory disorder that currently has no approved therapy. So first let's understand the IgG4-related diseases. It's rare. It's a chronic immune-mediated condition with a prevalence of 5.3 per 100,000 patients in the U.S. It's B-cell driven, characterized by mass lesions that are rich in CD19-positive B cells, and that's important, that drive inflammation and fibrosis. Hey Luke, what molecule do you think inibilizumab targets? Something on a B cell? CD19 in fact! So CD19-positive B cells are enriched in the lesions, and that is the target of inibilizumab. Is that also how you diagnose these? You biopsy them and find these CD19 cells? Actually, you usually stain for IgG4, but we'll get to that. Multi-organ impact can occur in this syndrome. It can affect nearly any organ system with multi-organ involvement typical of the disease, and

it causes progressive damage with disease flares that can lead to organ dysfunction and even failure if untreated. So you're going to pick up a theme in the kinds of diseases that are connected to IgG4-related disease. There's type 1 autoimmune pancreatitis, which is also known as lymphoplasmicidic sclerosing, pancreatitis, sclerosing cholangitis, mycelux disease, which is IgG4-related dacroadenitis and saladenitis. Aerytonitis, Dachloradenitis is inflammation of the lacrimal glands. Chronic Sclerosing, Dachloradenitis. Sclerosing Stale Aerytonitis which is also sometimes called a cut nurse tumor. Inflammatory Orbital Pseudo tumor which are fibrosclerotic changes on the tumor. Idiopathic Retroparent Nail Fibrosis also known as Ormand's disease. Chronic Sclerosing Aortitis and periaortitis. Rhydylsthyroditis which is characterized histopathologically by fibrosis. Rhydylpneumonitis and pulmonary inflammatory pseudotumors also have fibrosis as a prominent feature. IgG4 related kidney disease. Pacumeningitis which is inflammation and thickening of the dura matter. And hypophysitis with story form fibrosis that can replace the entire anterior pituitary tissue and compress adjacent structures. So as you've kind of been able to pick up, fibrosis is a common theme with these disease states. In fact- None of those sounded very much skin like though. I'm getting- What is a dermatologist going to notice? So I have a very like cute mnemonic that you can use to remember the skin lesions that can happen in IgG4 related dermatosis which is plasma puppy. So plasma puppy being you can have papules, lymphadenopathy, angiolymphoid hyperplasia with eosinophilia like lesions. You can have subcutaneous nodules, maculopapular eruptions, alopecia, purpura, urticaria vasculitis, psoriasis or eczema like lesions and ischemic digits. So plasma puppy with an eye at the end. Many of these- That's a lot of things you can get. You can and they're all on the skin. It seems like this should be on our list of things that can cause most morphologies along with CTCL and syphilis and sarcoid. I think that you're right. We could add this to what we sometimes call the STEC7 or something like that. The list of things you can pop out to say, "Oh, it could be in any differential." Like you know, people bring forward lupus or CTCL or sarcoid, things like that. So fibroinflammatory vasculopathy can occur, which is an obliterative phlebitis and you can also have intimal fibrosis and stenosis and occlusion. So a lot of fibrotic features. The difference between angiolimphoid hyperplasia with eosinophilia and IgG4-related dermatosis that has ALHE-like lesions are that the normal angiolimphoid hyperplasia with eosinophilia is considered kind of a benign vascular neoplasm, whereas the IgG4-related disease is immune-mediated fibroinflammatory disease. You don't really tend to see the epithelioid endothelial cells in the IgG4-related disease and the steroform fibrosis is more common with IgG4-related dermatitis. You can see increased IgG4-positive plasma cells, but they're consistently elevated and usually more than 50

per high-power field with IgG4-related dermatosis, which is one of the ways you diagnose those. And then serum IgG4 can also be elevated along with usually some kind of systemic involvement with the IgG4-related dermatosis. So the challenges in treating this condition are that there are no approved therapies. There's nothing FDA approved to treat IgG4-related disease. Glucocorticoids are a mainstay of treatment. They can often induce rapid improvement of the skin and systemic disease, but of course, we can't keep patients on chronic glucocorticoids. And disease control is not maintained when steroids are tapered. We don't want to give patients the side effects of long-term steroids, so some kind of alternative therapy would be beneficial. Older patients often have conditions that will be worsened by glucocorticoids, so there's a need for an effective therapeutic. Other steroids-bearing agents that are often used in the case of managing IgG4 at this point are rituximab. Rituximab is highly effective. It results in B-cell depletion and can induce remission and is especially useful in refractory disease. Azathioprine can be used as maintenance therapy, as can mycophenolate moffatil. Methotrexate is often used for cutaneous disease, especially if there's something resembling paniculitis or morphia. Encyclophosamide can be used in severe or organ-threatening cases. They designed the Mitigate trial to evaluate the utility of inabalizumab, which is kind of like a younger, faster, stronger rituximab. So you think of rituximab as this hero that's depleting the B-cells as early as one week. Inabalizumab actually works within three to five days. It is a humanized monoclonal antibody that targets CD19, and that's a protein that's expressed on a broad range of B-cells, including naive B-cells, memory B-cells, and plasma blasts. Plasma blasts play a central role in the pathogenesis of IgG4-related diseases, including its cutaneous manifestations, which are referred to as IgG4-related dermatoses. The cells drive the fibroinflammatory process that characterizes the disease, and plasma blasts are immature proliferative precursors of plasma cells. They express CD19, CD38, and CD27 in MHC class 2, but they do not express CD20, so they are not depleted by rituximab. So the cell that's most responsible for the IgG4-related dermatoses is only indirectly suppressed by rituximab, which at this stage is the most efficacious treatment that has been available for IgG4-related disease. So they took 135 patients with active IgG4-related diseases, infecting at least two organ systems, randomized them one-to-one to Inabalizumab or placebo for 52 weeks, and they treated them with 300 milligrams of IV infusions on days 1, 15, and week 26. Their primary endpoint was time to first treat it adjudicated disease, FLAIR, and the patients were allowed to use glucocorticoids because you couldn't just not treat these patients. They would lose the function of the organ systems involved, so they have to be able to be treated for their FLAIRs. Plasma blasts produce a large amount of IgG4 antibodies, and they may also

secrete TGF-beta and other fibrogenic cytokines that drive the story form fibrosis that can kind of characterize the disease. So for the drugs that do work for the IgG4-related dermatoses, the effect on the plasma blast is important to consider. Rituximab has an indirect reduction over time as it depletes the CD20-positive precursors of the plasma blasts. Inabalizumab is an anti-CD19, directly targets plasma blasts, and may offer deeper and faster suppression. Glucocorticoids temporarily suppress plasma blast activity, but they relapse as soon as you taper the patients. So they had impressive efficacy results in their patients with IgG4-related disease. 68 were assigned to Inabalizumab, 67 assigned to placebo. The treatment with Inabalizumab reduced the FLAIR risk. Only 10% of patients or 7 participants in the Inabalizumab group had one FLAIR compared with 40 participants or 60% of the patients in the placebo group. So the hazard ratio was 0.13. Remember a hazard ratio less than 1 reflects that you're protecting the patients from the likelihood of that occurring. The confidence interval was 0.06 to 0.28, so a very significant confidence interval that did not even get close to capturing 1. If you have a confidence interval that captures 1 with a hazard ratio, that means effectively the risk is the same with or without the treatment. So definitely a risk reduction with treatment with Inabalizumab. When you looked at patients having FLAIR-free treatment complete remissions, more patients in the Inabalizumab group had FLAIR-free treatment-free complete remission with an odds ratio of 4.68. So that is a great thing to have. You want to have a greater risk of having a FLAIR-free treatment-free complete remission. Like that's very exciting to not have to be on therapy and not experience disease FLAIR. So their confidence interval there was 2.21 to 9.91. The key secondary points were the annualized FLAIR rate and then the FLAIR-free treatment complete remission as well as glucocorticoid-free remission at week 52. So for patients who had treatment with the Inabalizumab, we had 58.8% of them that achieved a FLAIR-free glucocorticoid-free complete remission at week 52 compared to 22.4% in the placebo arm. They published in the article a very interesting Kaplan-Meier survival curve where they showed the probability of FLAIR and it didn't look like any Kaplan-Meier survival curve I've ever seen before because it's basically almost completely horizontal, meaning nobody is having a FLAIR. There's like a few little jigs down on the line at the very beginning and then it's just flat line and then at week 365, at day 365, it goes straight down. The reason for that is that the event, the median time to event in the Inabalizumab actually couldn't be determined because less than half of the participants had an event by the end of the treatment period. So at nominal day 365, they kind of just terminated the analysis for their safety reasons. So they had great survival without FLAIR in the treated group. They were also able to significantly reduce their glucocorticoid use in the Inabalizumab group. They had 118 milligrams of

glucocorticoid use over the total of the study. In the placebo group, it was 10 times that. 1384 milligrams mean glucocorticoid use per participant and 90% of patients in Inabalizumab group were able to discontinue glucocorticoids. There were serious adverse events during the treatment period. There was about twice as many adverse events in the Inabalizumab group as there were in patients who received placebo. Those included things like COVID-19, lymphopenia, and UTI. There were actually more infusion reactions with the placebo than with the active drug, which was very interesting. And in overall adverse events, they were similar in both groups, 97% in Inabalizumab, 98% in placebo. For serious adverse events, they looked at things like cytopenia, lymphopenia. Those were higher in the group treated with a drug that targets a part of the immune system, which makes sense. And there was a higher rate of COVID, lymphopenia, and UTIs. Other side effects were actually similar between groups, including importantly herpes zoster and patients did not experience any really significant anemia or other cytopenias. So the implication here is this is the first proven therapy, CD19 targeted B cell depletion as effective treatment, 87% reduction in disease flares compared to placebo. It was significantly lower glucocorticoid requirements in the patients who were treated with Inabalizumab, so very steroid-sparing agent. And they're going into a three-year open label period to establish an ongoing safety profile. So very exciting to learn about a therapeutic option for these patients. These IgG4-related dermatoses and internal organ involvement diseases can be very debilitating and severe and progressive. And that fibroinflammatory process can be very relentless. So having something that can control that is a very exciting thing. So I don't think we dermatologists are going to be prescribing Inabalizumab, but I think this is useful because we should, or at least I should, be better at recognizing things that could be IgG4-related disease. I've heard that term bandied about for the past few years. So I'm aware that it's out there, and so this is kind of a nice review of what it can look like to us. And it sounds like I should do a biopsy with DIF if I want to diagnose it. You know, there's lots of different ways to diagnose it. Immunostains can be performed on biopsied tissue. They're reliable on formalin-fixed tissue. So long as you help your pathologist to be aware of your concern for that, especially if there are other organ systems involved, you know, things that I think would be low-hanging fruit would be a patient that comes to you with abnormal thyroid function, somebody who's had serious problems with gallbladder disease, if they have something that acts and sounds a little bit like mycolaic's disease, or maybe that's kind of like odd, show grins and maybe there's sort of a Morphea-like component to it. Any of those things could tip you off to the possibility that this patient is dealing with an IgG4-related dermatosis. Lots of internal organ disease, sort of a nebulous unwellness that you can sense an inflammatory process, an

auto-inflammatory process is responsible for. I think that that's one of the things you could certainly consider. As a dermatopathologist, a lot of lymphoplasmicidic infiltrates that are dense along with the storiform fibrosis should raise our awareness of the potential for IgG4-related disease. And you don't necessarily DIF then, you can just stain for these B cells? Yeah, you can just do regular immunohistochemistry and stain for IgG4, and that can help you to make the diagnosis. And I think it's useful to know that this is out there, and perhaps we could work with our colleagues in rheumatology or whoever it is who manages this medicine to get it for our patients if we can. It looks like it's available, it looks like it was actually approved in 2020 for some other disease called neuromyelitis optica spectrum disorder. It's expensive, as you might guess, about $250,000 a year, it looks like. Yeah, I think like any biologic, there's going to definitely be a cost barrier for patients. But as this is a relentless progressive fibroinflammatory disease, I think advocacy is an appropriate place to stand on that. And I'm very excited that there is something that works for it because it can kind of eat people alive. So it is a great thing to have a therapy for. Well, I think we've got time for one more article here. So I'm going to talk about one from the journal Pediatric Dermatology called Early-onset Hypertension Associated with Extensive Cutaneous Capillary Malformations Harboring Post-Zygotic Variants in GNAK and GNA11. The authors include Olivia Davies and Beth Drolet. So last time, I think I talked about a couple articles that came from the Pre-AAD SPD meeting. This is another one. This one reports early-onset hypertension in 5 out of 29 patients with port wine stains, which are also called capillary malformations. And the upshot is that we should be checking our patients, if they have fairly extensive port wine stains, for hypertension. Just by checking their blood pressure. And if we do find hypertension, we should refer them to nephrology. So this paper defined early-onset hypertension as hypertension before age 55, which seems like a strange definition, because apparently the average age of hypertension diagnosis in the United States is 46. Nevertheless, the patients in this series who had hypertension were of average age 15, which definitely does seem early. The patients with hypertension all had fairly extensive capillary malformations that all involved the trunk and affected anywhere from 9 to 56% of their body surface. Some of them did have Sturge-Weber syndrome. The five patients who had hypertension also had renal ultrasounds. And three of those five had abnormalities on renal ultrasound. And some of them have additional workups, probably driven by nephrology, including MRAs and CT scans, as well as measurements of renin levels. You know, outside my usual approach to patients with capillary malformations. But why capillary malformations might be associated with hypertension is a bit of a question mark. There are various hypotheses they mention in this article. Perhaps the abnormal vasculature of the capillary malformation itself is

extensive enough that it affects systemic circulation. Hard for the blood to move through there and need some extra force, maybe. The mutations involved. So remember, the mutations involved in capillary malformations are GNAQ, which is also called GNAQ, and GNA11. Remember, it's codon 183. Have a role in calcium homeostasis, which could somehow lead to hypertension, I guess. Remember patients with Sturge-Weber syndrome with calcification in the brain. So calcium is somehow involved. Patients in those genes could also be involved in angiogenesis, and they may also mediate the adrenal aldosterone response, apparently. Apparently the estimated prevalence of hypertension in children is around 6%, so the number in this series, which was 17% of their patients, does indeed seem higher than what we might expect from a random sampling. It's easy enough to check blood pressure. And their definition of hypertension is "two or more measurements of systolic blood pressure over 130 or diastolic blood pressure above 80, or two or more measurements of systolic or diastolic blood pressure above 95th percentile for children under 13 years of age." So once you hit 13, you can use the adult criteria, which is 130 over 80. Under that, you should look up what the 95th percentile is. And I recall from med school and from a friend of mine who's a cardiologist that you want people to be like, "Sitting comfortably in a chair, not doing any activities, feet flat on the floor for five minutes before you actually check their blood pressure." He, a couple years ago, was telling me he has been removing hypertension diagnoses from his patients just because their measurements weren't taken properly. There you go. If you've got somebody with a big port wine stain, especially if it involves their trunk and affects at least 10% of their body surface, you should be probably checking them to see if they have high blood pressure. Well I think that's all the time we have for today, friends. So thanks for joining us. And today we learned about superficial radiation treatment, especially the image guided version with Dr. Jake Scott. We learned about lipidema. We learned about enabalizumab for IgG4 related disease. And we also learned that patients with big port wine stains can have hypertension associated with it. So thanks to our institutions, of course, thanks to the University of Utah for supporting the podcast, and thanks to Texas Tech for lending us Michelle. And thank you to all the members of Team Dermasphere. They are a dedicated group of medical and pre-medical students who keep things moving along behind the scenes. We are very grateful to them. They include Jordan Easterling, Austin Callister, Justin Lyon, Kripa Ahuja, Hiral Patel, Karen Akul, Mary Tidwell, Mary Matthew, and Allison Roker. Thanks very much for all that you guys do, such as keeping our website up to date. You can find us at dermaspherepodcast.com, which has links to all of the original articles that we discussed and houses our entire archive. You can also find us on social media. Again, thanks to the team. We are on X, Instagram, and Facebook. And you can find some of

us hanging out at the University of Utah Dermatology Echo Sessions, the second Friday of every month. Love to see you there. Guess that's all. You can also find us right back here in two weeks. We'll see you then.