Optimizing Outcomes for Patients With Soft-Tissue Sarcomas Through the Multidisciplinary Medical Oncology/Radiation/Surgical Team Approach

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INTRODUCER My name is Gabrielle Zecha. I am from Seattle Cancer Care Alliance where I am a PA. Our next session is a wonderful example of multidisciplinary collaborative approach, entitled "Optimizing Outcomes for Patients With Soft Tissue Sarcomas Trough the Multidisciplinary Oncology Radiation and Surgical Approach." Please join me in welcoming David Johnson from Moffitt Cancer Center, Dr. Arash Naghavi, also from Moffitt, and Princess Leah, also known as Leah Clark from Moffitt Cancer Center. Thank you.

DAVID JOHNSON Good morning to everybody. We definitely appreciate the audience coming to listen to this. We find it a very fascinating topic to discuss this morning. I definitely wanted to take some time out to thank *JADPRO* for inviting us and also APSHO for inviting us as well to this conference. I know that I am enjoying it, and hopefully you guys are enjoying it, and this will even solidify that for you as we go through talking about our interesting topic today. You guys have been able to see the learning objectives and stuff. Mainly what we want to talk about today is this multidisciplinary approach to treating this very rare disease of soft tissue sarcomas. We are going to talk about surgery, we are going to talk about radiation, and we are going to talk about chemotherapy. Not only are you going to see the multidisciplinary approach, you are going to see the multiprofessional approach as well. As you see, I am here with two outstanding colleagues of mine, Leah Clark, NP, and Dr. Arash Naghavi, MD. It does take a

team to treat these patients. It is a very rare disease, and we will go through the whole process. These are our financial disclosures.

Let's talk about sarcomas. I don't know how many people deal with sarcomas out there, but let's start with the basics a little bit so we know where we are playing from. Everything comes from the Greek, so "sarc" meaning fish-like, and "oma" meaning tumor. So this is a fish-like tumor, that's how they describe it. And the reason why it gets that description is because when we surgically resect it, it does look like that. It looks like raw fish, so to speak. The tissue does not look like its normal process in the human body, so it comes up with that type of name. They are transformed cells from a mesenchymal origin. They get their name from their point of origin, so if you have a sarcoma starting in bone, you have an osteosarcoma. If you have a sarcoma starting in the fatty tissue, it is a liposarcoma. If it is on the vascular side, hemangioendothelioma. That is how we derive the names.

Soft tissue sarcomas are extremely rare. As you see, benign neoplasms from a mesenchymal origin are about 100 times more likely to have them than a malignant soft tissue sarcoma. You can have sarcomas that originate in the bone that make up a smaller percentage of the sarcomas. A larger percentage are made up from your soft tissues that we went over earlier. These are very rare diseases. You can see the statistics in 2015. We had about 11,000, almost 12,000 new cases of soft tissue sarcoma diagnosed. Put that into perspective: in the United States alone, breast cancers in that year were about 250,000. It just kind of depicts how rare this disease is. It is rare; however, it does make up

about 1% of all cancer deaths. In 2015 we had cancer deaths of approximately 5,000. In 2016, not a whole lot of difference. We had a little bit of increase in the numbers, about 12,000 new cases of soft tissue sarcomas and approximately 5,000 deaths. You can see by the pictorial that you have a 1:100,000 chance in getting a soft tissue sarcoma in somebody 20 years or older. As we get older, greater than 20 years, you have about a 7:100,000 chance of getting a soft tissue sarcoma, so extremely rare. Male to female ratio is pretty close, 1.2 to males. 1.0 to females. This is mainly a disease that we see prevalent more as we get into our older decades of life, 60, 70, 80, and sometimes even 90 year olds. They come in different sizes and shapes. They can be in your extremities, they can be in your trunk, they can be in your neck, they can be in your retroperitoneum. They can be pretty much anywhere in your body. So when we have a soft tissue sarcoma, or I should say a soft tissue mass, that presents on a patient, we need to be working it up appropriately and have this awareness that not everything is benign, even though we talked before about 100 times more mesenchymal origin cells, but we can have these malignant cells as well. We need to be aware of this. In fact, if you look at the delay in diagnosis in soft tissue sarcomas anywhere from about 3 to 6 months, we all know the quicker we can treat a cancer, the better outcomes we can have. So we need to have this awareness about these disease processes.

With the advent of the human genome being depicted, we have been able to find out different mutations in that genome that actually transform into certain soft tissue sarcomas. This has been very revolutionary in the way that we treat

our diseases now, particularly systemically with our chemotherapy, and Leah will talk more about this in the future, but if you went to the genomics lecture earlier, I think it was yesterday, they did a phenomenal job talking about mutations in cells and how the body tries to make that better, but if they cant, basically these cells can transform further getting into your soft tissue sarcoma development.

Let's talk about workup first. When we have somebody with a soft tissue mass that presents to us, we want to be aware. We want to not just slough it off and say, "Oh, that's a lipoma." We want to definitely work it up. We need to consider the age, we need to consider the location, we need to consider what is the functionality loss with that patient. If it is in an extremity, do they have any type of functionality loss? Talk about the skin, what does the overlying skin look like? History, history, history is very important, not just for soft tissue sarcomas, but for any of the cancers that we deal with out there; so history, very, very important. The next thing I would talk about would be imaging. Imaging is very important. X-rays, CT, MRI scan. It is going to help us determine whether or not this looks more malignant or more benign, so imaging is very key. But our gold standard to make the diagnosis is really biopsy. This is where the multi D approach comes into place. You need to have a dedicated musculoskeletal radiologist to go over that radiology. You need to have a dedicated pathologist that specializes, hopefully, in soft tissue sarcomas, because these are very difficult histological and radiological diagnoses to make on imaging and pathology, but our gold standard is really biopsy, and this is very key. We will talk about staging in just a little bit. Here is an interesting thing, when we talk about

the approach to working these patients up and stuff, we already talked about age, their symptomatology, where it is located. Remember age is very important. If I have somebody who is a teenager with a soft tissue mass, I am not thinking malignancy right off the get-go. But if I got somebody at 60, 70, 80 years old that has a soft tissue mass, certainly that becomes higher up on my differential, so age is very important. Radiographs are very important. Plain film x-rays can give us a lot of detail about what that mass is doing. And sometimes people will say, “Well, Dave, we get plain film x-rays for bone; we don’t really look at soft tissues in the plain film x-rays.” Plain film x-rays are relatively inexpensive to get. We all have access to plain film x-rays, so we want to go ahead and get that. We can see density with a soft tissue mass, we can see mineralization, and because of density and mineralization in those plain film x-rays, we can develop our differential and see whether or not this looks bad or not so bad to us. CT scans. We do get CT scans occasionally. Sometimes somebody needs to get a CT scan, they got shrapnel in their body, the have a defibrillator, they can’t get an MRI for whatever reason, and they get CT scans. This is a really great pictorial here where you see the soft tissue mass on the lateral aspect of somebody’s thigh. This is where your multidisciplinary team comes into play because you have your musculoskeletal radiologist telling you from a CT scan, yes this is a heterogeneic mass, it is big, it has a lot of different densities in it, and stuff like that. Biopsy with your musculoskeletal radiologist is very important because we need to get the yield that we want, so if we biopsy this area right here in the center, we are going to get normal fat. Does that give us a lot of information? It

actually tells somebody that if they do biopsy that area, it is a benign tumor. This is a little bit more intermediate grade and more hard grade. This is where our money is at right here. We want to talk with our musculoskeletal radiologist; this is where we want to do our biopsy, it gives us the highest yield for making that diagnosis. So, multidisciplinary approach here, and then also getting with the pathologist to go over that radiology as well to go over the presumptive diagnoses. MRI scan is really our gold standard here when looking at imaging. So with soft tissue sarcomas, on MRI scans usually the masses are about 4 cm or greater. They are dark on T1, bright on STIR signal, and bright on contrast. They are heterogeneic. They have a lot of different densities in the soft tissue masses. There is some necrosis sometimes with it. They have a pseudocapsule so you can trace your finger around it and say that's exactly where the mass is. You can see the heterogeneity of the mass; you can see the tissue necrosis here and stuff like that as well. Peritumoral edema you are going to see on a STIR weighted image. Here is your T1, here is your STIR weighted image, and here is your contrast enhanced image. You can look at it on axial. You can look at it on sagittal. You can look at it on coronal planes. It does not matter. But make sure you get those three images up: T1, STIR, and your contrast enhanced image. Very, very important to make this diagnosis. Here you can see on the STIR weighted image, which is our water weighted image, that same mass that we saw in the previous slide, you can see where the peritumoral edema is. Right here and some up right here, both proximally and distally. This is very important to work with your musculoskeletal radiologist, because from a surgical standpoint

this is important to know where that peritumoral edema is and it depicts what type of resection we are going to be doing.

Soft tissue sarcomas outlook. Poor prognosis: somebody that's older, somebody that's greater than 60 years old, somebody that has a higher grade tumor, a larger tumor, and sometimes even they have already been excised someplace else and they present with positive margins. These are all significant for poor prognosis.

When we talk about soft tissue sarcomas, I already told you there are about 12,000 diagnosed every year. There are over 70 different subtypes of soft tissue sarcomas, and they are treated just a little bit differently. That's what makes it so challenging to treat this disease, and that's why you need the multidisciplinary approach. You can see out of the 12,000, only 27% make up the most popular or most prevalent soft tissue sarcoma, which is your undifferentiated high-grade sarcoma, followed by liposarcoma and then finally leiomyosarcoma.

Let's talk about size with these tumors. Size does matter with soft tissue sarcomas. You can see the 5-year survival rate here. This is taking all comers, all histological subtypes, all grades. This is just totally looking at size, so if you have a tumor that is less than 5 cm, 75% chance of a 5-year survival. And you can see where the pictorial brings you down as you get a higher type of tumor as far as size goes.

Let's look at grade. Grade is very important as well. Remember we have three grades when we deal with soft tissue sarcomas. We have low grade, we

have intermediate grade, and we have high grade, high grade being a more aggressive tumor. This is taking all comers. This is taking all sizes, all histological subtypes, and just looking at grade as being a predictive value of overall survival as you can see there.

Let's talk about stage for a little bit. We do stage these tumors. We have stage I,II, III, and IV. Our stage I tumors are typically our lower grade, less than 5 cm tumors. These are low grade, less than 5 cm tumors. Stage II: these are our intermediate to higher grade tumors, still maybe around 5 cm, could be a little bit over, a little bit above 5 cm. They are more superficial type of tumors and they are more in the distal portions of your extremities. Stage III: still intermediate and high grade, but now your tumors are getting a little bit bigger, they are getting greater than 5 cm, and now they are more deep in your soft tissue and they are more in the proximal portions of your extremities and also into your retroperitoneum. Then stage IV would obviously be your metastatic disease. Here is your survival rate when looking at the stages, and it makes sense as we see down here, as we get into our stage III and IV we are definitely using modalities like radiation and chemotherapy, even in stage II radiation and chemotherapy as well. Our multidisciplinary approach.

Where do these metastasize to? Particularly the chest, they particularly metastasize to the chest. When I have someone with a newly diagnosed soft tissue sarcoma, I am going to get a CT scan of the chest, abdomen, and pelvis just to be thorough. I might have a histological diagnosis and stuff, but I have not removed the entire tumor, and sometimes we all know that our diagnoses

change. So I always start off with a CT scan of the chest, abdomen, and pelvis just to rule out metastatic disease. But once I finally get that tumor out and I have a definitive diagnosis, I might just go to a CT scan of the chest. The ones you need a CT scan of the chest, abdomen, and pelvis for are the myxoid liposarcomas, the synovial sarcomas, the rhabdomyosarcomas, and the angiosarcomas. Lymph node metastasis can occur as well, so we need to be aware of that. Lymph node metastasis needs to be looked at for some of our tumors. We use a pneumonic RACES: rhabdomyosarcoma, alveolar, angiosarcoma, clear cell sarcoma, epithelioid, and synovial, is what we need to be looking at those lymph nodes.

Multimodal approach: surgery, radiation, and chemotherapy. With surgery and radiation, we are talking about local control, so we can take the tumor out, hopefully we can get it under local control. We can use radiation. Sometimes we use radiation in conjunction with surgery; sometimes we use it as its own entity. We will go over that further as the talk goes on. Low-grade sarcomas: take the tumor out. This is a lower grade tumor, usually less than 5 cm, sometimes it can go up to 6 or 7 cm. We remove those. We rarely use any type of adjunctive radiation or chemotherapy. We may, in some instances, if the tumor is greater than 10 cm, or if this is a recurrent tumor in the surgical bed, or if removing the tumor was going to cause the patient a lot of functional loss, or they might have a positive margin from a previous resection. Most of the time we just take these out. High-grade soft tissue tumors: limb-sparing surgery is the key word here. We really try to limb-spare the surgery with extremity soft tissue sarcomas to not only

remove the cancer, but to provide the patient the best functionality as possible. This is important for our patients.

Let's talk about surgical margins for a little bit. These soft tissue sarcomas grow from an epicenter and they get bigger and bigger as time goes on. They push everything away from it. Remember it has a pseudocapsule, but also remember that it also has that peritumoral edema, which is important, because that is your reactive zone. Your reactive zone is where you can have microscopic disease that you can't pick up on your imaging. You need to be aware of that as a surgeon, so when you go in you do the appropriate surgery. The appropriate surgery for soft tissue sarcoma is there needs to be one normal cell between that surgeon and that tumor, that's a good margin, one cell. It's not like melanoma where you have to have 2 cm; you need one cell, so you need to be aware of this reactive zone and these satellite lesions. There are other types of resections you can do. You can certainly do a radical resection, removing an entire compartment, do a very wide resection, removing normal tissue, but here again, you translate that with a greater toxicity to the patient, and a greater functional limb loss. That is not what we are trying to accomplish here. We do not need to accomplish that. This is an example of a wide resection. You can see a normal muscle tissue, normal cuff of muscle around this tumor, it's in between our fingers, and that's typically what we do in our surgeries. With surgical margins, if we go back to that pictorial, obviously if we do a surgical resection and we are intralesional, we have a 100% chance of local recurrence. If we do a marginal resection, a 70%, a wide resection is about a 30% chance, and then radical or

amputation about 5%. So we need to be thinking about what type of surgery we need to do. This is where we think we want to be at, radical or amputation, but remember that is a high toxicity to the patient. It has a high functional limb loss with the patient, so can we do something to improve those numbers.

Here is some data that you can see goes with the local recurrence on a marginal resection versus a wide resection versus a radical or an amputation type of surgery for these tumors. I like to follow Enneking's data. I am from the University of Florida and Enneking is from the University of Florida. I like to follow his data, and you can see about a 4% chance of local recurrence, with a radical resection, 25% with a wide resection, and finally a marginal resection around 50% to 60%. This is the money slide here. We know we have a 30% chance of local recurrence by doing a marginal resection. Remember, because we are probably going to be in that reactive zone, where there is microscopic disease that we can't see very well on imaging. We may be able to see it a little bit better in surgery; we sometimes can see that edema. This is where we work very closely with our radiation oncologist because the radiation oncologist, sometimes we will even bring them into the operating room and say "Here is the surgical bed, here is where we think we are very close, here is where we think we are in the reactive zone, here is where I want you to concentrate your radiation." So with the roll of doing a wider resection, somewhere between a wide and a marginal resection, and the use of adjuvant radiation, we can get that recurrence breakdown to 7%, which is very comparable to radical resection and amputation, plus will preserve the patient's ability to function. This is where the

roll of radiation comes in. I will hand it over to Dr. Naghavi to go over further about that.

ARASH NAGHAVI Hello, today I am going to talk to you about the roll of radiation, and how does radiation work. The most common way that we treat with radiation for cancer is with external beam radiation. The way to think about it is, its kind of like a high-powered x-ray, and it can work both directly and indirectly to damage DNA. The most common mechanism by which it acts is the indirect method, and this is primarily dependent upon oxygen molecules neighboring the cancer, and it uses that to help cause damage to the DNA. Radiation can be done either externally or internally, known as brachytherapy. External beam radiation is a lot like, if you imagine flashlights that you beam on the area you want to treat. Now imagine hundreds of flashlights converging to one area. Where they converge is where it is going to be the hottest or highest amount of dose, with some neighboring dose in the structures adjacent to it, and that's a lot of times where you will get your toxicity. External beam radiation can either be given prior to surgery, also known as preoperative radiation or postop, and brachytherapy can be given as perioperative. It can either be done with immediate reconstruction, or stage reconstruction, which we will talk a little bit more about.

As Dave Johnson talked about with limb-sparing surgery, to try to help improve quality of life, they did notice an increase in the recurrence rate, so the addition of radiation in different trials have shown, the addition of radiation for

both high-grade and low-grade sarcomas improved local control by about 20%. This is a trial for external beam, and here is one from brachytherapy.

Now, preop versus postop radiation. There is a difference between the two. As I mentioned before, the primary way radiation works in the external beam setting is by affecting oxygen molecules. So in the preop setting there is less dose require to get the same amount of efficacy, and this is because in the preoperative setting the tumor is still well oxygenated, and you only require about 50 Gy, which is our unit of radiation measurement, compared to 66, somewhere between 60 and 66 Gy, in the postoperative setting. This could lead to potential toxicity benefit, both acute and long term. Fewer fractions in the preoperative setting, you require less fractions of radiation, so that's lower cost for the patient, and also improved patient convenience, because treatment is primarily daily for weeks on end, somewhere between 5 and 7 weeks. Smaller radiation volume: in the postoperative setting anywhere there is surgical manipulation is all at risk of tumor seeding, so we as radiation oncologists postoperatively have to cover those areas, whether it is the incision or the drain site, or anywhere that was surgically manipulated, so the volumes get larger, and there is evidence to show that with these larger volumes comes worse long-term sequelae. Preoperatively radiation can also potentially cause shrinkage of the tumor and an inflammatory fibrotic encapsulation of the tumor, which can improve the ability to get clear margins in the operation. There is some evidence to show that there is an improvement in disease control in the preoperative setting, and a lot of people believe it is because it is easier to identify the areas at risk preoperatively where

as postoperatively you don't have gross disease to help guide you. Other explanations include—as we talk about the age of immunotherapy, there is the idea that when you are treating preoperatively and you have this big gross disease that you are radiating, there is this rapid cell death, and with cell death you have a lot of tumor antigens that are presented in the blood, which may help activate the immune response, although theoretical, is one of the thoughts. Preoperative does have a detriment, and it's a big one. In the setting preoperatively, as you guys would imagine, radiation can stunt the growth of rapidly dividing cells, so when done before surgery, there is actually an increase in wound complication rate, almost double. And although it's rare, there is the possibility that when you radiate up front, the tumor could progress through radiation and could potentially make the patient unresectable.

Now we are going to talk about brachytherapy. This is the internal radiation that we were talking about. This starts off with, they have a resection, wide local excision, and we place catheters, spaced apart roughly a centimeter in the plain of the tumor bed. One thing I want to note is, IMRT, or intensity modulated radiation therapy, is probably one of the most sophisticated forms of radiation that we deliver. This is the external beam. As you can see, because you have radiation coming from all different angles, it nicely conforms around the tumor. This is the red here indicating the hottest area of radiation. But you see that there is dose scattered and sprayed all around, basically all of the normal tissue getting some radiation. With the internal radiation, since the catheters are inserted at the time of surgery, the radiation is delivered from within. So the

highest area of dose is right where the tumor was, and you see a rapid drop off in dose and almost no radiation to normal tissue.

Just to go over brachytherapy, because brachytherapy is probably the epitome of a multimodal approach between the surgeon and the radiation oncologist. In the operating room, the surgeon will remove the tumor, and that's when we come in and we discuss the areas that are highest risk of there being microscopic disease, and the surgeons will commonly put surgical clips to aid us in the area of where the tumor was, or even the extent of the resection done. The benefit is that you can directly visualize exactly the area at risk. The catheters can be positioned to help accommodate that area. The catheters are then positioned in the tumor bed and sewn with absorbable sutures and they are anchored to the skin with buttons. The two main techniques that are commonly utilized is the immediate reconstruction technique, also known as the traditional technique, where you see these catheters that are placed, and then there is a closure placed directly over it, whether it's a flap or a primary closure. Because there is actively healing tissue over the catheters, you have to wait about 5 days so that the radiation does not cause wound complications. The other form is staged reconstruction, which uses a temporary wound VAC, which acts as a closure, and you can start radiation as soon as the next day without any issues with wound healing, and actually we have retrospective data from our own institution showing that in patients that have been previously irradiated, it actually improved the wound complication rate. Then we do a CT simulation. That's when we do a CT scan of the area, kind of getting the lay of the land. We digitize the

catheters, we get an idea of the tumor bed, and you see here the clips are placed in the OR and we are able to digitize them, and that helps guide our treatment. We do radiation planning and this is where we allow our constraints, we try to meet our constraints and make sure that the volume at risk is covered. And I want to note here, you see how well this conforms to where it was, and all of the high-dose area is right here with no radiation dose to the remaining tissue. So you are able to spare bone, muscle, nerves, joints, etc.

Treatment delivery, we have an after loader and this has the radiation seed. This actually feeds the radiation bead through each of these catheters, for different varying amounts of time, to deliver a nice conformal dose to that area.

Toxicities. Historically, with older technologies, radiation was very large, had a high toxicity, very debilitating. You could see that patients would have this lymphedema that would last them a lifetime, and historically we treated about a 10 cm margin on the outside of the tumor. As technology has advanced, and as our techniques have advanced, we have lowered into about 5 cm in the 90s and pathology on amputations actually showed that about two-thirds of patients had microscopic disease outside of where the gross tumor was, and all of that was found within 4 cm of the gross disease. This has kind of guided us as radiation oncologists to ensure that our volumes, realistically is just the tumor plus about 4 cm. This is just an illustration between preoperative and postoperative. In preoperative radiation you have gross disease, and this gross disease, we do expansions about 4 cm, and this is the area that we treat, 4 cm along the length of the muscle and 1.5 cm axially. In the postop setting, you have the gross

disease, but then you have the entire surgical bed plus the site of incision and all of that is covered, and then an expansion is done on that. Toxicities associated with radiation, the most common being impaired wound healing, especially in the preoperative setting, edema, fibrosis, and decreased range of motion, and then less commonly fracture and peripheral nerve injury, and then also secondary malignancy, especially for your younger patients. There is about a 1% per year risk.

What do we do to help mitigate some of this toxicity? Appropriate patient selection. We would not want to do preoperative radiation on a patient who already has a lot of comorbidities for wound complication such as peripheral vascular disease, diabetes, etc. To mitigate acute toxicity, we could think about using wound VACs, using flaps, or sparing the flap when we are doing our radiation. There is also evidence to show that the time between preoperative radiation and surgery is important and trying to cut that to below 6 to 8 weeks can improve toxicity. Long term, one of the biggest things for long-term toxicity for a patient is the radiation treatment volumes that we use. As you would imagine, the larger the treatment volume, the more normal tissue is being treated, and the worse the toxicity. They actually have evidence showing there is worse fibrosis, joint stiffness, and edema. What we can do to help improve that is work in concert with our surgeons to get a better idea of the area that needs to be treated, to use some of the newer techniques like IMRT, and the also reducing the radiation dose. Doses over 60 Gy, which would be the postoperative dose,

have been associated with pain, edema, decreased range of motion, and fracture.

LEAH CLARK Just really until the 1970s, our modalities for treatment of metastatic soft tissue sarcomas were surgery and radiation. We had some systemic therapy by way of dacarbazine, but it really wasn't until the 1970s that we saw some new advances coming. You can see now, fast forward to today, we have a lot of things to talk about. We have combination therapy, we have some targeted therapies, and it was in 1973 that an Italian group, Dr. Bonadonna and his colleagues were studying the use of doxorubicin in many neoplasms. They were looking at lymphomas, breast cancers, sarcomas, and they included 64 patients who had soft tissue sarcoma. In this study, these patients received at least two doses of doxorubicin, and 21 of those patients, about a third of the patients who received doxorubicin who had soft tissue sarcoma had a response. If you know anything about Bonadonna and breast cancer, you know that he is pretty well known in that arena, but in sarcoma he is also known as the father of chemotherapy in sarcoma. One interesting thing about Adriamycin or doxorubicin is that it was developed in Italy, and so it is near the Adriatic Sea, and that's how the name Adriamycin came to be.

You can see in this timeline, and that's really what I'm going to talk about, is the timeline of development of systemic therapies for this disease, there are these big breaks. Between 1970 and 1980, we had dacarbazine and we had doxorubicin, and then in 1980 Patel at MD Anderson began working on ifosfamide, and it was approved for treatment of soft tissue sarcomas. Between

the 1980s and 2000 is a big break of 20 years, and during that time a lot of work was done with combination therapy with doxorubicin, ifosfamide, and maybe you all are familiar with the toxicities associated with those, cardiotoxicities of course with the doxorubicin, and neurotoxicities, cardio and renal toxicities with ifosfamide. They were really working at combination therapy, high-dose therapy, and then in 1997 Patel and his group began looking at high-dose ifosfamide for soft tissue sarcomas, looking at 14 mg/m^2. And in his research study at that time, they had 74 patients, half of them were bone sarcomas, the other half were soft tissue sarcomas, and they had four complete responders, 17 partial responders. But the bone sarcomas, the osteosarcomas, won out with about 40% response rates and 20% response rates for soft tissue sarcomas. You can really see there were some struggles with this very rare type of cancer through those 20 years until we saw a breakthrough in targeted therapy with a drug called imatinib. You all may know it, of course, in treatment of CLL. Gastrointestinal stromal tumors were originally thought to derive from smooth muscle and they were considered part of the leiomyosarcoma family. However, as time went on they were studied and were showing some ultrastructural evidence of autonomic neural differentiation. Now they are thought to originate from interstitial cells of Cajal, or at least differentiate into them, because the express see KIT, and/or CD34. This is the key that unlocked our thinking for sarcomas and we began to think, “What is happening genetically with these tumors? Where can we block the cell differentiation to stop tumor growth?” We found that about 70% to 80% of GIST express KIT and 70% of that expression is exon 11, but you can see the other

expressions here. They also express PDGFR alpha about 5% to 7% of the time, but we do have wild-type GIST as well; 10% to 15% patients have wild-type GIST. Imatinib came on the forefront in 2002, big breakthrough, approved for adjuvant therapy for locally advanced unresectable and metastatic GIST. Demetri and his colleagues in 2002 looked at the efficacy and safety of imatinib in doses of 400 mg and 600 mg, and they found about a 54% partial response, 41% stable disease. And what's really exciting is, that for the first time in the treatment of a soft tissue sarcoma, we saw median survivals that were very meaningful, 9 to 12 months.

Toxicities. I was saying it would be great just to talk for an hour on these therapies, but because I think many of you are familiar with imatinib you might know, peripheral edema, facial edema, periorbital edema. We have our patients take, and give them some counseling about, low salt diet, making sure they are very well hydrated, and compression stockings, elevating their extremities, and then sometimes we use diuretics, but we find that it is difficult to control this, and it leads to weight gain, which is very troubling for patients. Usually I do look at their thyroid function, and for men I will look at their testosterone, but beyond that sometimes I have to refer them to endocrine for a workup of weight gain, and usually this is chalked up to the extra fluid accumulation that they have. I have this one patient who tries very hard to maintain her weight, but with the fluid accumulation on imatinib she is not able to, and she has been on imatinib for 3 years after resection without any evidence of recurrence of her disease. Of course, the imatinib has nausea, vomiting, diarrhea, weight loss, sometimes

some unexplained abdominal pain. And then I didn't include slides on sunitinib and regorafenib, which are second and third line for patients who develop resistance to imatinib. After 2002 we have another break of time, 10 years forward till we find novel therapy with pazopanib, then also trabectedin, eribulin 2015, and then olaratumab in late 2016. Pazopanib is a multityrosine kinase inhibitor. It is FDA indicated for patients with advanced soft tissue sarcoma having previously received sarcoma. European studies showed that these patients had a medial progression-free survival of 4.6 months for pazopanib, and 1.6 months for placebo. The overall survival rate for patients on pazopanib was 12.5 and placebo was 10.7. You can see in the research study these patients had a fair amount of fatigue, diarrhea, nausea, weight loss. I always say we should market this for weight loss, but I don't think we'd have any takers because it's so toxic. Also, hypopigmentation, so patients don't lose their hair, but they do have their hair turn very brightly white grey. Hypertension and cardiovascular disorders are prevalent with this drug. We ask patients to take their blood pressure once a day and keep a log, if it gets above 140/90 to give us a call. We start conservatively depending on the blood pressure readings with diuretic, hydrochlorothiazide, or we will add an ACE inhibitor. Sometimes, if that is not working, I will switch to Norvasc, but beyond that sometimes I do refer out to our cardiologists—we have an oncology cardiologist right in our clinic—and have a full workup. It's always very important to help mitigate and control the underlying cardiovascular disease if they have that as a comorbidity as well. The GI toxicities of this can be very troubling per patients, hand-foot syndrome as well.

Pazopanib is given in 200 mg tablets. In renal cell carcinoma, the typical dose is 800 mg a day and it's fairly well tolerated. For some unknown reason, that we are not sure of, 800 mg is rarely tolerated in patients with soft tissue sarcoma. Generally we start with 200 mg, or 400 mg, and titrate up every 2 to 4 weeks by 200 mg. We usually get to about 600 mg. In the time that I have been working in sarcoma, I have one patient who has been able to tolerate long-term 800 mg of pazopanib. Trabectedin came on the scene in 2015. It's an alkylating agent that bends the DNA helix via the groove guanine. It perturbs the cell cycle, gets it pretty aggravated and leads to cell death. The indications are for unresectable metastatic liposarcoma or leiomyosarcoma in patients that previously had doxorubicin or an anthracycline-containing regimen. It's given by a 24-hour infusion CADD pump. Patients come in and they have an infusion visit, they get hooked up to their pump, and they come back 24 hours later, they get unhooked and they receive pegfilgrastim.

Demetri and his colleagues in 2016 published a study of 518 patients, and the final results shows that trabectedin resulted in a 45% reduction of risk for disease progression. And the take home was that it was superior to dacarbazine in terms of disease control. Toxicities are nausea, nausea, and nausea. Chemotherapy-induced nausea. If you don't work very hard in controlling it for the first dose, patients get a learned response and then it's very difficult for subsequent doses. I think there is some experience with this drug and other cancer types, and we borrowed from that, and our patients receive palonosetron plus steroids on day 1, and then when they are unhooked they get aprepitant.

And with that type of regimen and aggressive control of their nausea, we have good success, and then of course they have Compazine and nausea going home. What's different about this drug is we have to watch carefully for rhabdomyolysis. So along with your studies that you look at prior to chemo, you have to draw a CK level.

Next novel therapy—2015 was a big year for soft tissue sarcomas—is eribulin. It's another marine animal. It is derived from a sponge. It is FDA indicated for metastatic liposarcoma, previously treated with anthracycline-based regimen. These have pretty short infusion times, about 15 minutes for the actual infusion, maybe only a couple hours up in the infusion center. Schoffski in 2016 and his colleagues published, and this really is important, because this is the first randomized phase 3 trial of a single-agent systemic therapy with an active control to show significant improvable in overall survival. So, we were pretty excited about eribulin. The overall survival, overall, across both types of sarcoma, was 13.5 months for eribulin and 11.5 for dacarbazine, progression-free survival was similar at 2.6 months, but the winner here was liposarcoma. You can see that the overall survival for liposarcoma was 15.6 months versus 8.4 in the dacarbazine group. Pretty well tolerated. I have a patient who is probably on cycle 12 with liposarcoma, very good quality of life, plays golf every day with his buddies. We have to look out for neutropenia and constipation with the drug.

Then in 2016 we all got excited about olaratumab in combination with doxorubicin. It's a monoclonal antibody. FDA breakthrough designation for soft tissue sarcoma. Tap published a study demonstrating progression-free survival

with the combination of doxorubicin and olaratumab of 6.6 months, versus doxorubicin alone 4.1 months. But the big news here was the overall survival was new. This was the first time we saw a big advance in overall survival for these patients. That just means more birthdays, more anniversaries, more graduations, very exciting news for soft tissue sarcoma work. But the overall survival for the combination was 26.5 months versus 14.7 months in the single-agent doxorubicin. What we learned is that the combination therapy really doesn't have any new or different side effects, except we think that headache is more prevalent in the combination, and neutropenia can be more severe and prolonged with the combination, but we don't see an increase in neutropenic fever. So you may have a few more delays in treatment, but you don't have the neutropenic fever component.

So where do we go from here? When you think about my timeline, you see these big breaks. We see 10 years, 12 years, 20 years in between. Let's just hope that since we started in 2012, we are on a roll. There are now clinical trials for sarcoma that involve vaccines. We are looking at immunotherapy. We are doing intratumoral immunotherapy, injections. We are looking at CAR T-cell therapy, and we are looking at tyrosine kinase inhibitors in combination with other targeted therapy and investigational agents. So let's hope that the long desert is behind us. Thank you.

ARASH NAGHAVI Just to kind of tie it all together, the surveillance for these patients by the NCCN guidelines is primarily separated by low-grade tumors and high grade. It's kind of base on the risk. As Dave talked about earlier,

the two areas that sarcomas commonly recur are locally, and distantly, and the most likely place for distant recurrence is in the lung. So the imaging that we do is to look at local recurrence and distant. For low-grade tumors, local imaging is about 3 to 6 months for about 2 to 3 years and then annually. You can change this based on their local recurrence risk. Patients that have positive margins, or multifocal disease, or recurrent disease, you may want to have them more frequently. In high-grade cancers, you would want to go more 3 to 4 months for the 2 years and then 6 months for 2 years and then annually. Again, you can adjust it based on their risk of recurrence. Then for chest imaging, probably every 6 to 12 months would be adequate, but for high grade, 3 to 6 months for the first 2 to 3 years, 6 months for 2 years and then annually.

Multidisciplinary care. Here we talk about the multidisciplinary management between radiation and surgery. This working together can help improve the patient's toxicity and quality of life. Some of the key features, just to highlight again is working with the surgeon to localize exactly where the tumor is, and discuss the areas that are at highest risk. This will allow us to use more concise treatment volumes which can lower their long term toxicity, but then also can help disease control, especially when trying to resect in areas that are difficult to obtain clear margins, such as abutting neurovascular bundles and in retroperitoneal sarcomas. Working with the medical oncologist, it is important that the radiation oncology and medical oncology work together, especially evaluating appropriate overlap in care, and managing hematologic issues. At the end of the day, it is patient-centered care. We have multidisciplinary tumor boards to talk

about the different treatment options that are available between the surgeon, the radiation oncology team, and the medical oncology team, but then at the end of the day, it is up to us to bring these options to the patient and to evaluate the patient's personal goals. What is it that they want out of their treatment? Coordinate toxicity care and follow-up between specialties.

To summarize, there are varied groups of tumors when for high grades, these are more your large, deep, fixed heterogenous tumors with necrosis and the treatment for these is a multimodality approach including surgery, chemotherapy, and radiation. In surveillance, you want to look for local recurrence and distant recurrence, and you adjust the frequency depending on their risk of recurrence. I just want to thank the entire sarcoma team, Dave and Princess Leah, and the entire group. Thank you.

DAVID JOHNSON It looks like we have about 5 minutes for a Q&A session. If anybody has any questions, please shout them up to us.

QUESTIONER When you talked about the olaratumab, no allergic reactions? Because we have a ton.

LEAH CLARK Have you had allergic reactions?

QUESTIONER Horrible, severe.

LEAH CLARK We prophylax and Benadryl prior.

QUESTIONER We do to. I just want to say it because you may not be in the same region, and I think its regionally just like it is with cetuximab, and I live in a region. So, if you live in a region where cetuximab is bad, you may have

the same problem with this. We have literally had to call our rapid response for people who have died. I mean, they came back, but they are bad reactions.

LEAH CLARK They are very dramatic when they occur, and we have not seen that many of them because we prophylax prior. But we do have our rapid response team ready to go if that happens.

QUESTIONER We prophylax significantly before and still have it. I think it's again, there must an area this works in. That was one of our physician's thoughts, that it was the same as you see with cetuximab.

LEAH CLARK Interesting.

QUESTIONER I was wondering, you were discussing the dramatic increase in overall survival with olaratumab, and I am wondering is that recommended first line, or are there therapies that they have to fail before they can get that?

LEAH CLARK No, in the research study, patients received up to eight cycles of combination with doxorubicin and olaratumab, and then after, they went on maintenance. And in the research study they did day 1, day 8 olaratumab off, after they had completed their doxorubicin component. Many of our patients come to us with already anthracycline exposure, so we have to look very carefully at their cumulative dose of radiation. We may not be able to get those eight doses in. Sometimes we are happy if we can get two doxorubicin, olaratumab to four, and then put them on maintenance therapy, olaratumab after that.

QUESTIONER Hello. Go Gators. You mentioned in the initial staging imaging component of their care, CT scans of the chest, abdomen, and pelvis versus and MRI. Is there any role for a PET scan as part of that initial staging?

LEAH CLARK Very good question.

ARASH NAGHAVI PET scan is currently for investigational use only. There are some studies to suggest that you can use PET in radiomics to help predict for outcome, but it is not commonly used, to answer your question.

QUESTIONER In breast cancer when they do needle localization with MRI, is there any role, you were talking about the extent of edema around the tumor? Can you mark it so that surgically you are a little more accurate? Or is the imaging just not there?

DAVE JOHNSON What we do is, in the combination with our radiation oncologists, we will bring Dr. Naghavi into the operating room and show him where that reactive zone is, and then we actually use tissue clips to mark that surrounding area. Not only can they see it when they simulate the patient at the end for the radiation, they can see where our borders were, but actually I bring him into the operating room so he can actually see where we want to concentrate that radiation to its fullest extent. It is that team approach. It is interesting when you talk about the edema, so obviously when a cancer first presents. there is a lot of surrounding edema to it and stuff. If we happen to do preop radiation to it, or they might have chemotherapy preoperatively, some of that edema, obviously if we get a good response, will go away. When we talk about our surgical resections, we try to go back to the original imaging and look at where that

edema was, so we can be outside that, because intraoperatively we are not going to be able to see that at this point.

ARASH NAGHAVI With the preoperative radiation, it's not a dose that's high enough to eradicate gross disease, but it is actually very good for microscopic disease. It does a pretty good job of sterilizing the area where the edema is. The surgical resection required does not become nearly as large.

DAVID JOHNSON Alright team, I think that does it for today. We are available afterwards if you need to. Have a great rest of your conference.

ARASH NAGHAVI Thanks for having us.

LEAH CLARK Thank you.

[END]