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Radiation therapy of sarcomas

Prof Haas: Hello everybody, my name is Rick Haas. I'm a radiation oncologist in The Netherlands Cancer Institute Amsterdam, and The Leiden University Medical Center. I cordially thank the European School of Oncology and especially Professor Paolo Casali from Milan to invite me today to present the role of Radiotherapy in Soft Tissue Sarcomas. What we are going to do in the next few minutes is highlight some challenges we face while treating sarcoma patients with radiation. First of all, we're going to talk about the timing. Are we going to do the radiotherapy before or after the operations? We're going to discuss the dose to use, the tools to provide that radiotherapy dose with. We are going to discuss whether we are going to give radiation only or whether we are going to combine it with chemotherapy or targeted agents. We are also going to highlight some sarcoma indications in which we provide exclusive irradiation without surgery. And in the end, I will briefly highlight the issue of radiation associated sarcomas. Still in 2021, most centers worldwide provide radiotherapy after surgery. And they do so, centers that choose this do so because they want to have a full pathology report on a heterogeneous sarcoma mass that is unaffected by prior radiotherapy. And if you do surgery first and then radiation, you will find fewer wound complications. So, in the setting where you choose for post-operative radiotherapy your rationale is mainly based on surgical endpoints. But what about the quality of life of the patients thus treated? If you perform surgery first and then, post-operative radiotherapy, your radiation fields need to be very large. And in these fields, the probability of having joints in the fields are quite extensive. And this translates one in one to a deficit in late function. The toxicity of these patients will be worse because these fields are so large, and that is because of the length of the surgical scar. Where in the beginning, the sarcoma itself was much smaller than the scar the surgeons have made. In 2002, the Canadian group published their SR-2 trial where they compared the at that time standard post-operative radiotherapy dose of 66 Gray to 50 Gray preoperative radiotherapy. The study was published in Lancet 2002 by Brian O'Sullivan. And at a median follow-up of 3.3 years, the early toxicity, being the wound complication rates in the preoperative arm, was higher than the post-operative arm. And for this reason, the study was prematurely closed. In the design of the trial the investigator group designated that if the difference between the two wound complication rates would be 15% or higher, the study needed to be closed. The study intended to recruit 266 patients but it was closed after 119. With longer follow-up, in a presentation in 2004 at CTOS/ASCO, with a follow-up of 6.9 years, we still acknowledged that the local control probability in both arms was equal. But at this point in time, you will see that the long-term toxicity after post-operative radiotherapy is increasing substantially from 26 to 36%. And the difference between the two arms is now statistically significant, 23% after preoperative radiotherapy, and 36% after postoperative radiotherapy. And these are the graphs. And they are typical for radiation. With longer follow-

up you will see that the curves diverge, and a diverging of the curves mean that if you have a toxicity profile, it usually gets worse over time. Now, what do we know for those patients who have a local failure with respect to the radiation field sizes? The Canadian group, the same group as who did the SR-2 trial, investigated in 2012, 780 patients among which 60 local relapses were found, only 7.7%. They investigated by an overlay of the MRI scans that had diagnosed the local relapse on top of the radiation fields. And they found that the majority of all these relapses were in the high-dose region, 82%. 3% were at the field edges and 50% were way out of the irradiation fields. This was the reason for the British sarcoma group to initiate the so-called Vortex trial. And the Vortex trial randomized different volumes of post-operative radiotherapy. To recollect, if you do post-operative radiotherapy, you start with a large field to a dose of 50 Gray, and you follow with a boost on a smaller area of another 16 Gray. The Vortex trial randomized this setting, a large volume, then a small volume, versus giving the entire dose of 66 Gray to the smaller volume. That's called the Vortex trial. The first results have been presented at ASCO several years ago, but to the best of my knowledge there's no full paper available yet. So, to conclude on the timing of radiation in the setting of the Canadian trial, with longer follow-up, preoperative radiotherapy is as good as post-operative radiotherapy from an efficacy point of view. And with longer follow-up, preoperative radiotherapy is even better than post-operative radiotherapy from a toxicity point of view. The Canadians are not the only one finding these results. These are the results from the MD Anderson Cancer Center in Houston, where they retrospectively analyzed the wound complication rate after pre versus post-operative radiotherapy in a non-randomized fashion. But they found, actually, exactly the same figures, 16 versus 34, and in the Canadian trial, 17 versus 35%. Published in Cancer in 2006. With respect to late complications, also, the Houston data are similar to the Canadian data, where the rates of long-term complications is related to the dose in the left panel with a cut of 60 Gray, and it's related to the timing of radiotherapy pre versus post in the right-hand. Obviously, these two features are interrelated, dose and timing, because in the preoperative setting you would never go over 50 Gray and therefore, all preoperative patients are in the below 60 Gray dosing. What dose do we need to provide local control for sarcoma patients? Well, in conventional radiotherapy for non-hematological cancers, let's say, rectal cancer or head and neck cancer, we use 46 to 50 Gray for microscopic disease and 66 to 70 Gray for macroscopic disease. But what is the evidence we actually have for sarcomas? Because we use the same dose-lengths. There's one subtype I would like to discuss with you. Let's see, myxoid liposarcomas. Several studies have shown that when you treat a myxoid liposarcoma by pre-operative radiotherapy, on treatment you will acknowledge a substantial volume reduction during and after pre-operative radiotherapy. And there, I highlighted some of the publications that have alluded to this. The question may arise, whether the vasculature of a myxoid liposarcomas has anything to do with this clinical observation in this clinical response, because within the myxoid liposarcoma you see intricate vascularity where all the tumor cells are very near to their nearest blood vessel and are very well-oxygenated and have very good supply of nutrients. When you treat a myxoid liposarcoma by pre-operative radiotherapy and during radiotherapy, you look by cone beam CTs to the volume of the residual VCs present. You will actually acknowledge already from the start of the third week, after 14 fractions, that there is a substantial decrease in the volume. When you look at the histology at diagnosis, on the upper-left panel, and after radiotherapy in the upper-right panel, and more in focus to the vasculature, you will acknowledge that the vasculature of the tumor that was abundantly open and present at start is now obliterated after pre-operative radiotherapy. This observation led us to the design of a phase II study investigating a lower radiotherapy dose, 18 X 2 Gray, and that study was called the DOREMY study. The DOREMY study has been published in JAMA Oncology, in 2020, and has been presented at the annual meeting of the Connective Tissue Oncology Society. The PhD students presented 79 patients being treated to 18 X 2 Gray pre-operative radiotherapy. At time of presentation and at time of publication, the median follow-up of the study was 25 months. The local control at two years was 100%, not a single local relapse after a reduced radiotherapy dose. And also, the wound complication rates went down. You would expect after 50 Gray, a 35% wound complication rate, but after 36 Gray, we observed a 17% wound complication rate. Now that is of value both for patients and for healthcare providers. This led us to the design of the DOREMY registry. It's an international web-based registry in which

real life data can be added on patients that are diagnosed with a myxoid liposarcoma and being treated for more metastatic disease. You can decide yourself whether you're going to treat the patient by surgery alone, by 25 Gray radiotherapy which is typically 5 X 5 Gray, or the previous phase II dose-level 18 X 2 Gray pre-operative radiotherapy to 36 Gray. The conventional 25 X 2 Gray pre-operative or even post-operative radiotherapy to a 60 to 66 Gray. When we have discussed now all these issues about radiation in the setting of sarcomas, all these studies are photon based. So, conventional linear accelerators. Is there any role for proton beam radiotherapy in setting of sarcomas? What hardware tools we use to provide our radiation dose to our patients? The typical example of the use of proton beam equipment for sarcoma patients is in the spine, the base of skull, and the sacrum. The typical diseases that are present there are the chordomas and the chondrosarcomas. And as an example here, the paper by Tom DeLaney from Harvard, published in 2009, showing the results after proton beam therapy alone for sarcomas around the spine, providing excellent local control and excellent overall survival. All these data have been summarized by Herman Suit in a paper and degree journal, in 2010, with several beam energies like proton beams and carbon ions with various doses but all, substantially, high. With various local control but in all, reasonably, high. And at the same time, a reasonably low late toxicity rates. I invite you to have a look at this paper by Herman Suit in the Radiotherapy Oncology Journal, in 2010. Also, what we have been discussing now is radiation only. When we will treat lung cancer or rectal cancer patients, usually we combine radiotherapy with systemic compounds, like chemotherapy or targeted agents. And there are several examples for these combined modality regimens, like cisplatin, taxanes, 5-FU, and temozolomide, but even more modern targeted agents, like monoclonal antibodies and tyrosine kinase inhibitors. These investigations have also been done in the setting of sarcomas. The world-famous regimen "MAID" is a combination of mesna, adriamycin, ifosfamide, and dacarbazine, inter-digitated with radiotherapy, by the way a quite toxic but effective regimen, has been published. And when you look at clinicaltrial.gov you will find several trial designs in which several compounds had been used, like sunitinib, sorafenib, pazopanib, bevacizumab, sirolimus and cabozantinib. My own investigations have been in the area of pazopanib and we will present our data shortly. What we also have discussed up to now is management of sarcoma patients in conjunction to surgery. Are there any indications where we treat our sarcoma patients, our soft tissue tumor patients, with radiation only? And yes, there are examples like the desmoid type fibromatosis and dermatofibrosarcoma protuberans. Obviously, outside the setting of surgery, in a palliative intent, we can also treat patients, usually, with a short-course in a somewhat hypo-fractionated regimen. And by doing so, we can alleviate pain. We can alleviate neurological symptoms by compression of nerves. We can diminish dyspnea, we can stop bleeding, but this is all palliation. In the setting of curative intent, we can look at desmoids and DFSP. Desmoid, the aggressive fibromatosis has been extensively investigated by the MD Anderson Cancer Center in Houston. Again, the publication in 2008, on 115 patients with a median follow-up of over 10 years. And some of these patients received radiation alone for gross disease, and some of them in combination with surgery. And this study provided a local control probability that it was equal in both study settings of about 75% at 10 years. The actuarial local control for these 115 patients is shown in the left panel, and the actuarial incidents of radiation related complications is in the right panel. Where you can see here very clearly that the red line with a dose constraint at 56 Gray has the lowest long-term toxicity profile. Whereas dose level of above 56 Gray, the black line, has a much higher chance of inducing toxicities. Again, looking at local control for the entire 115 patients and for the 41 treated by radiation alone, you can appreciate that age matters. Usually, the older patients have a higher local control. Probability, size matters. The dose doesn't matter. And if you look below and above 56 Gray, the local control probability of both regimens are more or less the same, but as shown in the previous slides the toxicity profile varies substantially. And also, in the 41 patients treated by radiation alone, the 56 Gray dose level doesn't matter whether you go below or above for local control but it does matter for long-term toxicity. The same dose-level has been investigated by the EORTC Soft Tissue and Bone Sarcoma Group, published in 2013, with 44 patients being treated with a median follow-up of 4.8 years and also, there, the local control-rates was 80% at three years. And also, there, the dose level was 56 Gray in 28 fractions or 2 Gray. So, based on the MD Anderson data, and based on the EORTC data, the current

golden standards for desmoids is 56 Gray. Exclusive radiation in the setting of dermatofibrosarcoma protuberans. Very scarce literature, but there is some available where Herman Suit treated these patients to the dose-level around 70 Gray and provided local control in a prolonged period of time with good to excellent outcome. In the management of inoperable DFSP cases there may be a role for imatinib in downsizing the tumor and then making these primary inoperable tumors operable, all these tumors that have shrunk amendable to definitive radiotherapy. What you can also consider in the setting of desmoids is the addition of nirogacestat which is a new gamma-secretase inhibitor currently under investigation for its clinical value in desmoids. Finally, I would like to discuss with you the radiation associated sarcomas, please call them radiation-associated. They are not radiation-induced sarcoma. We induce, as radiation oncologists, DNA damage. We do not induce tumors, that secondary tumors are associated to radiotherapy, that's the official term, radiation-associated sarcomas. When you look at the setting of let's say breast cancer, the incidence of finding a secondary sarcoma after breast cancer radiotherapy is in the vicinity of about 0.03 to 0.2%. They occur late, with a median latency time of about 15 years and they do very poorly. The overall survival at five years rarely exceeds 30%. The most prevalent histologies found in the setting of radiation associated sarcomas are the high-grade undifferentiated pleomorphic sarcomas and obviously, the angiosarcomas. The angiosarcomas are actually quite easy to diagnose. You can see them with your bare eyes. This is a patient that has been treated with a breast amputation and postoperative chest wall radiotherapy for her breast cancer 15 years ago. She developed a radiation associated angiosarcoma in the scar and was treated by re-irradiation in this setting in combination with hypothermia and providing excellent local control and good cosmesis. But in essence, if you find a patient with a radiation-associated sarcoma, let's say typically in the breasts, the management is surgery, if still feasible. The extension of these diseases are actually quite wide beyond what you see with the bare eye. In conclusion to put the entire presentation into perspective. We have thus discussed about the timing of radiotherapy. In case you have a large, deep seated, grade II to III sarcoma, preferably radiotherapy prior to surgery is the preferred option. And please educate your local surgeons to this mode of action. Yes, you will find more wound complication, but yes also in the long run, these patients fare better with a lower long-term toxicity profile. In case of the small or superficial or low-grade lesion, probably surgery alone is the best way, how to manage them. On the dose, in the postoperative setting we provide 45 to 50 Gray to the surgical area, the long fields and compassing the entire scar. And we continue with a boost on the primary tumor sites. We await the results of the British Vortex trial. In cases you use pre-operative radiotherapy, you get 50 Gray on the sarcoma mass only, and if you are dealing with a myxoid liposarcoma, please consider a lower-dose and participating in the DOREMY registry. Most of the radiotherapy, and most of the papers you will find are LINAC-based. So, photon-based treatments, but there are settings in which proton beam generators have been an advantage, let's say for the chordomas and the chondrosarcomas of base of skull, spine and sacrum, and the very rarely available carbon ion generators as in Japan and in Germany, they also provide good local control with good outcomes. In the setting of sarcoma still we are in an area in which we treat the patients by radiation only, which is not the case what we do in other kinds of cancers, but there have been investigations in the setting of sarcomas as well. And you can combine radiotherapy both in the pre-operative and in the postoperative setting, in combination with conventional chemotherapy, like adriamycin and ifosfamide, look at the papers from Milano, in Italy, they do so. There had been several studies investigating targeted agents and monoclonal antibodies. And the world of science is open there. We should do more to increase the efficacy of radiation or even use chemotherapy and targeted agents to lower the radiation dose. Exclusive radiation has been discussed in the setting of palliation of sarcoma patients and definitively, in the setting of desmoids. The golden standard dose level is 56 Gray. Radiation associated sarcomas are rare, but behave aggressively, should be managed if possible by surgery and possibly, there's a role for the combination of radiotherapy and hypothermia. Having said that, I thank you very much for your attention. I thank the European School of Oncology for inviting me to have this lecture today and I thank you again for your attention.