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The role of image-guided radiotherapy in cancer care

Prof Zips: Thank you very much, and it's my great pleasure to welcome you on this live e-session today, with the title "The role of image-guided radiotherapy in cancer care". Before I start to discuss some of the main points, I would like to show you my disclosure slide and I will discuss with you one of the main success stories of modern radiotherapy and that is the advantage we have done both with in-room imaging, IGRT, but also with the integration of both anatomical and functional imaging. And we know for those who are working in radiotherapy today, you know that radiotherapy is an image-guided treatment modality in all steps, from diagnosis to simulation, monitoring and follow-up. It is helping IGRT to make radiotherapy to the modality as we know it today, very precise, effective, and tolerable for the patients. And importantly, as I will show you examples, the development will not stop now, it just has started to increase the applications and opportunities that are coming with image-guided radiotherapy, which, in my mind, is one of the major approaches of radiotherapy towards personalized oncology or precision medicine. And if you want to read about this further, I refer you to this review article, which colleagues and myself have put together last year, and it's about the topic of today's session, and it gives you more details on some of the developments, and as you can read here, very famous heroes in the field of research and implementation of image-guided radiotherapy in the different fields, cone beam CT, Marcel Van Herk, for an example, brachytherapy and image guidance, Vincent Gregoire, Karin Haustermans for PET integration, MR guided radiotherapy, Jan Lagendijk and Ben Slotman, and others. If you interested, I would recommend to download this review for further reading and also, for further references into this very important area of research and implementation in clinical practice. Radiation oncology, due to its character as a local-regional treatment, has a very specific role in the era of precision medicine. And here's another review article I strongly recommend to read, about the concept, "How Radiotherapy Can Contribute to Precision Medicine," which means for radiotherapy, the right dose, for the right patient at every treatment. And there are two different principles, and one is the geometric precision. Where is the tumor, when I'm treating? So, that's the precision, the anatomical precision as precise as possible, as this allows to give safely radiation dose, and even increase radiation dose to break resistance, but the save time, to spare normal tissues. And of course, there are different examples, like particle therapy, that's the bottom panel, or multi-field or rotational, IMRT techniques, in order to achieve that, what we call the therapeutic window, between tumor response and normal tissue response. Apart part from this geometric concept, imaging can also serve as a biomarker. It gives information on the sensitivity of the tumor or the sensitivity of the normal tissues for individual patients. And instead of treating unselected population of patients, let's say all patients with stage 3 and 4-A head and neck cancer, with the same generic dose of chemo and radiation, we use molecular imaging, for example, and I will show you examples, to stratify patients according to risk groups. And here we combine two things, imaging as a biomarker, but also, imaging to guide precision radiotherapy. And I think that makes radiotherapy and the integration of advanced imaging

unique, if you compare that, for example, with other approaches like in medical oncology of giving personalized drugs or with surgery. So, it's a unique contribution of advanced imaging into radiation oncology towards precision medicine, personalized oncology. And this is laid out nicely in this conceptual review paper, five years ago. So, let's give you an example from the first patient we have treated at our 1.5 Tesla MRI. This was a young patient with recurrent prostate cancer, PSA rise, after prostatectomy, after salvage radiotherapy, again, PSA rise. And the reason for that was a small lymph node metastasis in the pelvis, jus next to the rectum in the very close to the pre-irradiated area. You can imagine that it was very difficult to find this small lesion, surgery deemed not possible because it's too small to find and that was discussed in the tumor board and SBRT was recommended. And of course, we can use high-resolution CT and MRI for the simulation, but in the workflow, when it comes to SBRT, high delivery of large single doses, in this case, we prescribed 5 X 8 Gray. Close to the preview radiated area, you see the challenge with cone beam CT. We have difficulties to find a target, and also, difficulties to see where's the critical structure in this case, the rectum. And this is an MRI that was taken at the MR Linac. And you'll see this here. This is the lesion, this is the target, 5 millimeters, and this is the critical structure, the rectum. This is the radiation plan. So, while we do the planning online while the patient is on the table, we have full control by advanced high-contrast soft tissue image to see where the target is, to do the treatment planning and to deliver the treatment and use motion monitoring, and use motion monitoring, doesn't work the movie. Use motion monitoring to see whether the target remains in the PDV for the whole procedure. So, this is kind of a future wish in where we can push anatomical imaging to very high-contrast with CT or MRI, and not only in the simulation phase, but also during the online adaptive planning and delivery, to know exactly where a tumor is, what dose the tumor gets, and what is the dose to the critical structures next to the target. So, I think that's pretty much the future, where are we going towards, to more online, real time, while the patient is on the table, adaptive workflows with advanced image modalities, for example, MRI or synthetic CT. When we talk about biomarker, and for radiotherapy trials, we face a number of challenges because you will ask yourself, in your practice, how many imaging biomarkers we are using today in our routine? Not many, if at all, although, there is a large number of papers and studies published, and this is due to some of the challenges which are described here. For integration, implementation of an imaging biomarker in radiotherapy, we need technical validation, biological and clinical validation, and, as they are often very expensive, we need cost-effective analysis to provide evidence that that's worth the money and the effort. And usually, there are three phases, and this is phase 1. This is the discovery. So, observations in experimental settings, small animals and small groups of patients, very small group, often only 10 or 20. And this is explorative to say, "Okay, there might be potential for this-and-this biomarker to select patients with persistent tumors in a certain tumor type." And then, there is the first translational gap, and I will talk about this, and this is to make an imaging biomarker reliable, robust, quantitative, to be used in multi-institutional settings, not only just in one institution. So, that's about the quality assurance of a biomarker before we can use this in the next step, which then is setting up hypothesis driven trials, and we can discuss which kind of trials that might be, registries, prospective collection of data, randomized trials. We can discuss this later. In the end, an imaging biomarker is routinely used in the management of patients with cancer. And there is a large number of candidates and you know all that, that's using PET, FDG, hypoxia PET, proliferation PET, F-FLT; the same for MRI, perfusion, effusion-rated imaging as a surrogate for cellularity, how dense the tumor is, how many tumor's cells are there, relaxometry in T1/T2 mapping, ASL, arterial spin labeling to measure perfusion. And also in CT, there are perfusion characteristics, and also, more and more the use and investigation into radiomics using imaging parameters to profile characteristics, to characterize the tissue tumor on normal tissues. Before I continue, I would like to remind you that you always have the opportunity to interrupt me and to type in urgent questions during my talk in the Q&A button, the arrow, the red arrow shows you that in the window, and to type in, and Pier Francesco might interrupt me and ask me, if I'm not seeing it, or, of course, also possible to discuss the points of my talk at the end of my presentation. So, let's discuss a few examples where advanced imaging has improved patient care in radiotherapy. And here's one example for FDG PET/CT, for radiotherapy planning, for head and neck cancer. And this is a recent type, in a group of more than 600 patients with head

and neck cancer, they have used in about half of the patients FDG baseline PET to better define gross tumor volume, especially, particularly, to define whether or not, a lymph node is regarded metastatic or not. By doing so, in using strict criteria, they could show that the use of FDG PET/CT for target definition in the simulation step can improve local-regional control compared to CT-only workflow. So, this is an example where functional imaging helps to increase the anatomical target delineation. So, we use the information of glucose metabolism to better decide whether or not a lymph node is a metastasis or not and that translates into better local control compared to standard CT during the workflow. Here's another example where FDG PET/CT was used to improve the treatment of non-small cell lung cancer, last year published, multi-center trial, where patients with non-small cell lung cancer have been randomized, either to receive a non-PET-based standard therapy off the gross tumor volume, including the mediastinum or PET/CT was used to better define the involved primary and lymph node metastases, but if there was no indication of disease in the mediastinum, the mediastinum was not electively irradiated, but instead, more radiation dose was given to the primary and to the lymph node metastasis. So, dose escalation was facilitated by a better target volume concept, through the use of FDG PET/CT and the planning process in lung cancer patients. And this trial could demonstrate that with this approach using FDG in the planning, better, more precise target volume delineation, and using this for dose escalation in the patients increased the chance of local control in this group of patients, and you see the Kaplan Meier curves for local-regional progression. So, 40% in the standard group progressed, whereas only about 20% in the experimental group with the dose escalation showed a progression. So, a clear indication that the use of advanced imaging might facilitate more individualized approaches with dose escalation only to the tumor. Another example where advanced imaging is used to improve clinical outcome is the FLAME trial, that has been published this year. And this is a study in prostate cancer, where multi-parametric MRI in a standardized way, was used to define the target volume and also, the dominant lesion in the prostate. And there, a T2 and a diffusion weighted imaging was performed with a lot of quality assurance among the different institutions and the multi-institutional settings, so, that's the step 2. That wasn't the gap 2 I was referring in one of the earlier slides, that was rolled out and then patients were given either standard 77 dose escalated or standard dose, or a focal boost to the dominant lesion up to 95% with the guidance of pre-therapeutic baseline multi-parametric MRI. And the toxicity data have been published earlier, and that shows that within the constraints the toxicity was comparable in both arms, and low, and you can see that the biochemical disease-free survival of the five years is improved in the focal boost group. So, that's another example where advanced imaging, in this case MRI is used to increase safely radiation dose to the tumor, and by doing that, improving outcome of cancer patients. Now, if we go beyond the point that we use advanced imaging to know where the tumor is and which lymph nodes are there and why the dominant lesion is, and so on, and it's mostly anatomical information. If we go beyond this point, and say, "Okay, we want to use imaging also as a biomarker to understand which patient is resistant and who is not resistant," to individualize our treatment, hypoxia imaging is one of the examples that have been investigated over many years by different groups, and there are many trials supporting the evidence that patients with high uptake of hypoxia tracers and PET in the tumors, for example, in head and neck cancer. These patients have a higher-risk of local failure of the chemo-radiation and they have also a higher-risk of distant metastasis. So, hypoxia imaging, clearly, is able to profile the characteristics of a tumor in a group of patients and to predict outcome of the patient. So, that's the prognostic value and that's well been shown for several tumor types and by several groups, so, there is good evidence that this is the case. The next step, of course, would then be to base an intervention on this prognostic group, and so to say, that if the tumor is hypoxic by PET, give extra dose to the hypoxic regions, for example, by using an approach that is called dose painting. So, giving dose to voxels that are more hypoxic compared to voxels that are not hypoxic, and that has been done in the Tübingen Group, and by Steven Weitz and Daniela Thorwarth, and we currently prepare the manuscript for submission and that was done in a total of 54 patients, and what you can see here is a preliminary evaluation, and patients with no hypoxia in the local regional advanced head and neck cancers, they have a local control rate of 100%, so, very good prognosis, obviously, candidates for de-escalation. When there is hypoxia in the tumor measurable by PET, patients have a local recurrence rate of about 30%. If these

patients were randomized to the group to receive an extra dose of 10% to the hypoxic soft volume of the tumor by dose painting, the curve is slightly increased to a lower rate of local recurrence. And here, you see another problem of many of the trials, they are underpowered. So, this difference between dose escalation and non-dose escalation is statistically not significant, although, the data is suggestive that extra dose, even if it's only 10%, can break resistance if we use hypoxia imaging to stratify patients for individualized dose prescriptions. It did not work well in lung cancer, there's also a randomized trial from the French Group where the prognostic value could be shown but the intervention, using a dose escalation strategy based on the imaging, was not effective to increase local control in non-small cell lung cancer, and that might be for several reasons we may want to discuss. There's quite some evidence that the power or the prognostic and predictive value of biomarkers can be increased if we not only measure before we start the treatment, but if we do several measurements throughout the treatment, so, for example, in week one, two, three, and four. So, it looks that we get additional information, if we know and profile how the tumors respond, for example, with regard to re-oxygenation. There are tumors that have high-levels of hypoxia at baseline, but they re-oxygenate during fractionated irradiation and others not, and it looks that this additional information might enhance the value of imaging biomarkers for individualized radiotherapy. And one of the prominent examples here is an example also in head and neck cancer, but in this case, it's dose de-escalation. And this is the work from Memorial Sloan Kettering, where they have used hypoxia imaging FMISO PET in HPV positive oropharyngeal patients, and if there was no FMSIO in the lymph nodes at baseline or in week-1, they de-escalated the radiation dose to these lymph nodes to 30 Gray. So, a substantial decrease based on the knowledge that if in addition to HPV positive, if hypoxia is not present or results very early during treatment, it allows, and the data actually indicates that, it allows a safe reduction of radiation dose without losing local tumor control. Certainly, an approach that should be further evaluated in, for example, randomized trials to individualize the treatment here by detoxification and de-escalation using negative information from hypoxia scans. Similar to PET, there is a lot of information on functional imaging using Magnetic Resonance Imaging, MRI. And this has been shown for head and neck cancer and not all the data is very clear in ADC, what time point, what protocol, there are many issues and bringing that into a clinical scenario, there are also attempts to use not only MRI but maybe a combination of MRI and PET to further enhance the prognostic value. The same time, also the burden for the patient increases with multiple investigations, and also, the cost increases. So, it needs to be well investigated what the added value of additional power meters. And I will not go into details, furthermore, here we have done some research in better understanding what you detect with hypoxia PET and what you detect with functional MR, and as you can imagine, and would expect these volumes within a tumor do not match one to one, so, you get additional information with each technology, imaging technology you add to the portfolio. And the second step, the second phase is the validation, and there, medical physics and MO physics, and PET physics play a huge role in developing together with the doctors, protocols, QA protocol for the imaging in RT position, for example, using the mask, geometrical accuracy, quantitative imaging is a big, big challenge today to make a measurement of today, so reliable that you would measure the same, the next day, to re-test technology. Radiation oncologists need the very high precision of the imaging signal, so, distortions inaccuracies are detrimental because we want to put the dose exactly where we've seen the dose needed to be. And this is a kind of different thinking also for our colleagues in diagnostic radiology because they have different approaches towards imaging and also, different requirements for what we need to do. And we have done this whole trail of development for integration of functional MR for head and neck cancer in our Institute, and we have assessed all the different steps with coils and different masks. And we have translated this to online adaptive hybrid MR-Linac, and we have done some pilot studies in patients with head and neck cancer, for example, to combine functional MR with high-precision real-time adaptive radiotherapy. And I will not go into more details here because of time. And the last two slides I would like to share is to think where the future of advanced imaging for personalized radiation oncology is, and that in my mind is clearly the use of adaptive approaches. So, maybe, from day-to-day or once per week, not only use anatomical information, but also, response information from functional imaging, and response can be shrinkage of the tumor but it can also be that hypoxia result. At the same time, it can

be early imaging signals in normal tissues, for example, the mucosa and the rectum give a certain signal early in MRI, that precedes symptoms of the patients. So, the integration of multiple layers of imaging information and other inflammation into the daily decision, where to put what dose. So, remember the initial concept of personalized radiation oncology, the right dose, for the right patient at every treatment session. And this is a circle of improvement, possibly at every treatment session, and this, of course, has the challenge of what a human can handle, of how many parameters, how fast we can handle it. And that clearly opens the door for the integration of automation and AI driven workflows. And we have just published an example of an autonomous unsupervised planning pipeline for a patient with prostate cancer, where the first human interface was when the patient was on the MR-Linac to receive an adaptive treatment for his prostate cancer, whereas all other steps before that were fully autonomous without human interface, totally AI driven. So, that certainly shows that it's feasible, it's thinkable to more integrate and use automation and AI tools to implement adaptive radiotherapy with function and advanced imaging in clinical radiotherapy, and these are my conclusions. And as you can read here, I hope I could make the point that IGRT is a major contribution of radiotherapy to modern oncology. It increases local tumor control, it decreases toxicity, and it has a major and large opportunity and capacity for bringing personalized approaches to precision medicine to a better radiotherapy by adaptive tools, imaging tools, and advanced radiotherapy delivery. And with this, I would shortly mention the group here in Tübingen, who contributes to our research program, and I would like to thank you for your attention and I'm happy to take questions.

Prof Franco: So, thanks a lot, Daniel, excellent, excellent talk as always. And of course, to the audience, we are more than happy to receive your feedback, suggestion, questions, burning questions, we will be very happy to have your take on it. So, first, as message, I would strongly advise to read the two reviews papers that Daniel cited, the first one on molecular oncology, first name, Vincent Gregoire and last name, Daniel Zips, and also, the review on natural cancer reviews, first author, Michael Baumann, because they are very, very elegant actually, and very, very comprehensive, so, it's a very nice overview on the present of EGRT and on the future perspective, so, I'm sure it will be a very interesting read and very, very helpful for everyone. This was just like, I guess, sometimes to see if some burning questions would pop up, otherwise, we can start the discussion, Daniel, if you agree on that.

Prof Zips: Yes, go ahead.

Prof Franco: Yeah, I was interested in your opinion about the two morphological methodologies where you can use EGRT. So, we have computer tomography-based IGRT, and MR-based IGRT. So, they're quite different in terms of technicalities, also, in terms of informative contribution. So, computer tomography, I think it's really relevant, it has a really relevant role and beneficial clinical role in the development of radiation therapy. Some may think that delivery is crucial being conformal, using IMRT is crucial, and of course, we all know that it is, but, of course, also, being accurate and precise when delivering the dose is very important. And I think computed tomography cone beam CT, in particular, plays a crucial role in this, and also disseminating some very important techniques such as SBRT, Frameless SBRT, so, we want to hear your take on this, on how relevant is cone beam CT for EGRT.

Prof Zips: Yeah, I totally agree with you. So, we should not forget that the implementation and establishment of in-room cone-beam CT paved the way for many innovations in radiotherapy. As you mentioned already, IMRT, clinicians would not feel comfortable to deliver very irregular doses to spare normal tissues and to better target the tumor without having reasonable, good control where the patient is positioned, about where the delivery is. So, the precession of delivery, as you said, is not only the ability to shape the dose distribution, it is also to bring it exactly where it is. And this has led to novel target volume concept. This has led to increased radiation dose, dose-escalation without increased toxicity, and this has led also to a wide use of SBRT or radiosurgery, non-invasive procedures, and that is now available in many institutions, and so, a large group of patients has access to these technologies. So, that's really a success story, and even with CT, cone beam CT, there is still a lot of developments and improvements ongoing, and I mentioned synthetic CT,

for example, there are adaptive workflows, also, based on CT, or many things you also can learn from CT, and that's radiomics ongoing and so on and so forth. So, by far, CT has not reached the end of development to be better used in personalized radiotherapy. And of course, the radiation dose, that is extra used for imaging that has to be taken into account, but that depends very much on the patient's situation and so on and so forth. And CT has certainly, limitations, and there are clearly indications where higher soft tissue contrast is desirable, and one example is liver metastasis. So, in our experience, the use of MRI on an MR-Linac facilitates liver mets SBRT without markers. So, in most of the patients we have selected, we were able to see without contrast enhanced agent, to see, actually, the lesion in the workflow. So, while the patient is on the table, allowing real-time treatment planning and having control of the dose delivery. So, there are certain indications where MR gifts better anatomical imaging for higher precision in the simulation and also, in the delivery and monitoring process, and we use this widely already. And there are certainly indications where CT is doing a perfect job. MR brings the opportunity, of course, of functional imaging, and the jury is out whether this is needed to be integrated in a real-time workflow, or whether also offline functional MR can be used and integrated into, and so-called offline workflow integrated in adaptive boost strategies. So, that is a current research question, but this is one of the opportunities that comes with MR in IGRT.

Prof Franco: Yeah. Yeah, I kind of agree with you, I mean, MR, it's like more recent, more let's say catchy, I would say, it gives you different, different geometrical information, probably, of course, better in specific sub-site, it's very useful for online adaptive and to monitor some, and of course, but it has the added value of being able to provide you with some biological texture of the tumor. Of course, this has to be validating clinical setting, but it's a very interesting field of research and a very good possibility that MR may offer. I will take advantage of one question that is available on the QA, questioned by Arun and who is asking, "What is the optimal time for early response assessment for treatment adaptation? Does it vary with different body size and type of tumors?" Which is of course, an interesting question that is dealing basically, with adaptive radiotherapy and adaptation of the treatment, which, of course, is made possible by the enhancement of the bio images that we now have. So, yeah.

Prof Zips: Yeah, that's a very good question, and, of course, an area of research and as is already indicated in the question, it varies from tumor type to tumor type and it also, varies from patient to patient. What we generally observe is that already within week 1, maybe, at the end of week 1, we already see signals of, for example, changing cellularity or resolvement of hypoxia. And that continues then to week 2 and week 3. At later time points, some of the tumors shrink quite remarkably and it becomes increasingly difficult to measure with functional imaging in the remaining tumor, plus there is surrounding inflammation by the radiation-induced mucositis, for example. So, there is a kind of an optimum that you extract a robust signal, large enough to say it's a responder or a non-responder, where you have later in treatment shrinkage, and other things that might increase the noise and makes it more difficult to measure. As a rule of thumb, from many studies, it looks that week 2 and 3 is kind of an optimum for a general population. Ideally, one would have the opportunity to measure, for example, once per week, and then make a decision on a certain change in the signal and then, put that in intervention. And for some patients, the intervention can be in week 1, and for others in week 2 and for others in week 3. This idea of picking a time point for a population, also, comes from the simple fact of logistics, and it's simply not affordable to send large numbers of patients in multi-center settings every week to get a PET scan or some advanced imaging, it's simply impossible. Maybe, with MR in an integrated workflow, it will be possible a sequential imaging, and to have more degrees of freedom to really put a timely individualized intervention on the individual tumor, and maybe, at different time points, and ideally in an adaptive workflow, at every time point, the intervention is adapted to the signal when you measure. So, ideally, maybe, in the future, every day, the dose prescription is based on a biological profiling of the tumor of the day, just before you deliver the beam.

Prof Franco: Which is quite fascinating, right?

Prof Zips: I don't think it's impossible, I don't think, and we have to go step-by-step, and of course, it needs, as this is a new paradigm, this comes with new dose and fractionation concept that needs to be conducted and validated in clinical trials. There, I personally think a registry would not be sufficient to do that.

Prof Franco: Yeah, I mean, the sky is the limit, so, who knows for sure. I think this thing you were mentioning that you might take sequential images also, allows you to use Delta parameters, like so, difference from previous images compared to the ones that may allow you also to run this type of trial in a multi-center settings, because when you use data parameters, you're less likely to be influenced by the acquisition parameter, because you're basically measuring a difference within images that are acquired with the same parameters, so, I think it might help in the multicentric implementation of clinical trial with this. I think, Daniel, if you agree, we can discuss a little bit about dose escalation, which is, of course, a nice concept, a quite classical concept. You have your tumor control probability curve with the stiffness, and you can have an holistic approach, you can decide to dose-escalate the whole tumor volume, that may come with some toxicity, or you can be more specific and try to target a specific biological target, and there, of course, you need to identify the target, depending on the methodology you want to use. You can address cell density, you can address proliferation, you can address hypoxia. And of course, this can be different depending on the clinical scenario and the oncological context. The clinical data about dose escalation are different, depending on the settings; some are positive, let's say the FLAME trial for prostate, head and neck, the PET boost for lung and some other are negative, basically, esophageal cancer, a holistic approach for the boost in lung cancer. So, what is your take on dose escalation? What is the situation now, and where are we going?

Prof Zips: Yeah. First of all, I think dose escalation is a valid approach to improve radiotherapy. This is what we have in our hands to prescribe the right dose, and it's not necessarily only be dose escalation, it can be also dose de-escalation. So, ideally, we would not prescribe generic doses to histological types and ignoring the heterogeneity. So, I think it's a valid concept and that needs to be further pursued. But it's challenging. You mentioned the tumor control probability curve, the S-phase probabilistic curve. If you think of it, there will be always patients with a low-risk of tumor recurrence, and they will not benefit from dose escalation. There will always be patients with very large tumors, they will also not benefit from dose escalation, in the range, what we can give without excessive toxicity. You probably have a intermediate group of patients who will likely benefit from a certain dose escalation, and this type of selection of patients further challenges the problem of small studies. If you further stratify to pick the patient-group, makes it more complicated to really demonstrate the benefit of dose escalation that can be given. And this is one of the problems the trials suffer from the negative trials. Another problem is of course, toxicity. You cannot break every treatment resistance with increased radiation dose. There always will be tumors that are so resistant, that you simply cannot give the dose you would need, and these are patients who might benefit from combinations with immunotherapy, hypertonia, chemo or whatever. So, that's a further layer of stratification. And the next step then, of course, is the choice of the best biomarker. And there are many, many issues, and we mentioned quality assurance, robustness, also, access that multi center trials are possible to recruit sufficient patient numbers. So, there is actually a lot of knowledge already in our community and also published, and the hope, of course, is that with refinement of technology and also, with refinement of health technology evaluation in different settings, plus a better understanding of the tumor biology and access to technologies like MR, and MR is certainly, virtually available everywhere. It can be made available to a larger group of patients, to address these burning questions on to what extent we can increase radiation dose to tumors without the problems, for example, with excessive heart toxicity, which might be a problem in esophageal cancer, in central lung cancer and so on. So, I don't think that dose escalation is a failed concept. And we should not talk about only about escalation, also talk about de-escalation, and imaging is the potentially perfect biomarker to guide this intrinsic tool that we have in our hands. We could not give away.

Prof Franco: Yeah, I mean, we talk a lot about personalization of treatment, right? And that applies also to radiotherapy, give the patient the right dose, or escalate, where there's the need to escalate and de-escalate,

the need to de-escalate, so, it's the same concept of precision medicine and precision in radiotherapy, so, I agree with you. One last question, if there is no question coming from the audience, is about methodology. So, whenever, where you want to create clinical evidence for a new technology that is available for our patients, we have a trade-off. So, we have a new technology that will have a life, which will probably be short, because there will be innovation, so, the technology might change in a short time, but at the same time, when we run clinical trials, we tend to need long-term clinical data. So, we have a technology that will soon expire, and we need to create data on a long-term. So, this is of course a trade-off that somehow raise some methodological questions. So, in your opinion, what is the best way from a methodological perspective to assess the validity and the evidence of a new technology? Is it like the classical prospective randomized trial? Is an observational study, or a tumor registry? Is it the model-based approach as in the Netherlands for protons, the right way to select patients and then, maybe, randomized thereafter? So, what is your take on it?

Prof Zips: Yeah, so, as you mentioned already, health technology evaluation has different tools. There is not one methodology that fits to every application, and we should remind ourselves that many innovations in radiotherapy, evolutionary just came in and have not only rarely be evaluated in randomized trials, but we use it every day because it's so obvious, that that makes our treatment better. So, we have to be conscious about limited resources, every innovation, every new technology, and so on, increases the costs, increases the efforts, the resources we needed, and also potentially, could put the patient at risk. So, new technologies, like a new drug needs to be evaluated using a methodology that is well-accepted and established, and that people are using and have proper knowledge about it. And the model-based approach, which is used for head and neck cancer and proton evaluation in the Netherlands, that's a perfect example of patient selection, based on predicted benefit, and then, randomize the patients to show less toxicity. A perfect model that might be also a role model for a very expensive new technology in a type of disease where such clearly defined NTCP-TCP relationship exists. But that's not the case for all clinical situations and not the case for all tumor types. If it comes to a completely new concept of dose fractionation, like dose escalation based on hypoxia imaging, that, of course, requires ultimately, a phase III trial to show the benefit of a new intervention. If it comes to the integration of a new technology for cone beam CT, and in certain, maybe adoptive approaches on certain protocols, then, even I think in large prospective predefined cohorts, we already can learn a lot to develop and derive hypotheses that might then be the basis for later randomized interventional trials. So, I think we have to play on... or use different methodologies, depending on the question, and there's also a lot of literature and knowledge in our community about the challenges of health technology evaluation.

Prof Franco: Yeah, and the other consideration, I think, Daniel, is that sometimes, we already have real-life data there, and so, if we could find a way to collect and to properly analyze, this could be also very informative, and particularly in the setting of a health technology that this could be irrelevant, I think. But you are right. Depending on the setting, the different methodological approaches can be integrated for the...

Prof Zips: I agree with you. Ideally, we would collect the information of every patient, we do, we basically do. But we're not there in making the data usable and interchangeable, interpretable, and so on, but with AI, radiomics and automation, I think that that will be a major source of new knowledge and improvements for cancer treatment. Basically, for every patient and radiotherapy department can part of this and outside of interventional trials to be a knowledge based to improve on a daily basis, if you know what you're doing, and what your neighbor did, and you can learn from others, and it has been shown in principle that that's possible, but also, to generate new hypotheses on observations if you collect data and compare outcomes of different settings.

Prof Franco: Yeah, so, exciting time for radiational ecologists, basically.

Prof Zips: Exactly.

Prof Franco: Good. So, I think we are running out of time, so, if there's no other questions from the audience, I think we can close the session. I want to thank Daniel for the excellent talk, very educational and very interesting, as always, and I want to thank everyone for attending this nice session, and thanks to ESO for the educational program is offered on a daily basis to everyone. Thank you everyone.

Prof Zips: Thank you very much, have a nice evening, ciao.

Prof Franco: Bye, bye.