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Cardiac ablation with radiotherapy

Dr Krug: Hi, good evening. I'm very happy to be here, and to present on the topic of cardiac ablation with radiotherapy. This is a topic that is very rapidly evolving and is at the interception of radiation oncology and cardiology, actually. So, these are my conflicts of interest. Maybe, the main important point is that I'm a radiation oncologist, so, I will present on this topic from the viewpoint of radiation oncology, and I will try to address and to demonstrate also, of course, standpoints from cardiology as well, as good as I can. So, I'm going to give an introduction to the topic, and then, I'm going to present on clinical results and also, on preclinical experiments. It looks like it's the wrong way around, I'll explain later why I will start with the clinical results and then, go to the preclinical experiments. And then, I'm going to speak on open questions on this very rapidly evolving topic, and then, discuss also ongoing clinical trials. Of course, feel free to ask questions and add them in the chats. As long as there are no burning questions that need addressing, we will discuss this in the end together with Professor Franco. So, cardiac ablation with radiotherapy, mostly concerns patients with not oncological diseases, but with diseases that are mainly treated by cardiologists. It's mainly patients with ventricular tachycardia. This is an arrhythmia disorder that is arising from the great heart chambers, the ventricles of the heart. And this is a very important topic because ventricular tachycardia may lead to ventricular fibrillation and to sudden cardiac death. This ventricular tachycardia may arise in patients that are otherwise perfectly healthy, for example, in the setting of genetic conditions, but mostly, this affects patients with structural heart diseases, mainly those with ischemic cardiomyopathy resulting from myocardial infarction. And then there are patients that have dilated cardiomyopathy for different reasons, for example, due to viral myocarditis or exposure to chemotherapy in the past. And then, I also highlighted this in red. Very rarely, there are patients with intracardiac tumours, either tumours arising from the heart or metastasis to the heart that may result in ventricular tachycardia. This as well as an intersection between cardiology and oncology or radiation oncology in specific. And the management of those patients with ventricular tachycardia includes the use of anti-arrhythmic drugs. Often these patients also get an implantable cardioverter defibrillator that can detect this ventricular tachycardia and can stop this either by delivering a shock or by over-pacing this arrhythmia. And then, if drug therapy, ICD placement, is still not resolving its freedom from ventricular tachycardia, then, there's the option to do a catheter ablation, I will explain this on the next slide. So, to briefly demonstrate what we're talking about, I've here a short clip and animation of ventricular tachycardia from experimental animal models. So, they created a scar in the myocardium that in a patient could also resolve, for example, from myocardial infarction. And you can see here, the conduction, the electrical conduction in the myocardium and here, in the middle, we have the scar. And the problem that is causing this ventricular tachycardia is that you have different conduction velocities in the myocardium. So, you have the normal conduction in the healthy myocardium and in the scar, actually, you have a slower conduction and then, this can result in this circulating arrhythmia that leads to ventricular fibrillation and to contractions of the ventricle that don't result in relevant blood output. So, you can see this here again, so, this is the scar in the middle, and then, this is the slow conduction channel and that results in this circulating arrhythmia. You can actually map this arrhythmia by using a catheter that is situated in the ventricle, and you can also do a voltage mapping of the myocardium and can demonstrate here in red, the scar tissue compared to the healthy myocardium that is shown here in violet. And here, these areas, where you have the green yellowish colours, these are the border zones of the scar, where also this arrhythmia often arises and where these channels of slow conduction can occur. And with catheter ablation, actually in the same session, we're doing this mapping of either the running ventricular tachycardia or this voltage mapping also in sinus rhythm, you can then apply, for example, radiofrequency ablation either from within the ventricle or also, from the epicardium to stop these channels. This also results in scar formation actually, and this can terminate also this arrhythmia. There's also the possibility to noninvasively map this ventricular tachycardia by using electrocardiogram. You can see here, this is the best using many electrodes, much more than you use in a standard ECG. And then, you can use these electrocardiograms and map them to the body surface, and then, also visualise this ventricular tachycardia. This is interesting also from the standpoint of radiation oncology because this allows the whole procedure to be conducted noninvasively. I will later address this again. So, the problem with catheter ablation is that even if you use it, still a lot of patients will suffer from VT recurrence later on. This is just an overview of randomised controlled trials from catheter ablation for ventricular tachycardia. All of these patients had ICD placement before, and also, all of these patients had drug therapy for their ventricular tachycardia. You can see here that ablation is superior in terms of freedom from ventricular tachycardia, but still, even with ablation often 30 to 50% recur during the first year after catheter ablation. So, what is now the connection to radiation oncology? Stereotactic body radiotherapy, of course, is very commonly used in oncology for the treatment of either oligometastatic disease in the lung, liver, bone, for example, but also, for primary tumours, for example, early-stage lung cancer, prostate cancer. And the concept is to use a high precision radiotherapy technique to deliver radiotherapy to clearly define target volume with often one or very few fractions and achieve a high biologically dose. And this has been used for the treatment of intracardiac tumours in the past. Of course, this is very rare and there are only very few case series of SBRT for the treatment of either primary heart tumours, for example, cardiac angiosarcoma, or metastasis to the heart. I've listed here some of these case series that often involved only a single patient and the doses that were used were typically a bit less than what was used, for example, for lung or liver metastasis, but still the treatment was, in general, very well-tolerated although the follow-up was short and in most of the cases local control could be achieved for these patients. There was actually one case report, this one here from Lausanne, where the patient also had ventricular tachycardia resulting from a metastasis to the heart and local control was achieved and freedom from ventricular tachycardia as well. Again, please feel free to submit questions via the chat that we can discuss them at the end of the talk. So, for radiotherapy to patients with cardiac arrhythmia, the whole concept is different than stereotactic body radiotherapy for tumours, because in these patients, you don't have an actual treatment volume or area that you can define on a CT scan and even on other imaging, it's often very difficult to actually see what you're treating. So, you are relying on data from the mapping of this ventricular tachycardia. This is then transferred to the traditional planning CT scan, and then, you try to integrate the information from cardiology and electrophysiology, and then, define this target area using this information, and then, create a treatment plan that is then, again, very similar to what we are used in radiation oncology, and also, the delivery of radiation itself is not that different than compared to oligometastatic disease. When you're talking about the precision, of course, you have to integrate data on motion, especially, respiratory motion and maybe also cardiac motion to precisely deliver this. So, most of the experience, actually, is from Washington University in St. Louis in the USA. Actually, they were not the first to deliver the treatment. So, there had been two case reports, single patient case reports from Stanford and from the Czech Republic, and patients were treated in 2012 and 2014. However, this topic really gained traction in 2017 when a case series of five patients was published from the colleagues, Cuculich and Robinson from Washington University in St. Louis. And what they could demonstrate is that by giving a single dose of 25 Gy to the arrhythmic substrate in the myocardium, that patients who had longstanding history of ventricular tachycardia, and had had multiple catheter ablations, that had an ICD, had different antiarrhythmic drugs, and that had very frequent ventricular tachycardia episodes, that these patients could be very successfully treated with SBRT to this region. You can see here; this is the frequency per-month of ventricular tachycardia episodes per patients. So, these coloured lines are the five patients. This was the time-point of treatment, and you can see that over two months after treatment, the ventricular tachycardia episodes almost completely subsided, and that many patients could actually stop antiarrhythmic medication. And the same was seen for ICD shocks, and that is something that is very important for patients because the delivery of this ICD shock can be very traumatising and is limiting to quality of life as well. And you can also see here that this was dramatically reduced to zero over the month after treatment and the same also for this antitachycardia pacing by the ICD. So, this generated a lot of interest worldwide in this topic, and the colleagues from Washington University published a prospective trial one year later of 19 patients with treatment refractory ventricular tachycardia that were also treated with stereotactic body radiotherapy in one session with 25 Gy to the treatment area. And again, could demonstrate that the number of ventricular tachycardia episodes could be dramatically reduced. This is the number of episodes six months before and six months after treatment. And with these 19 patients, they could also demonstrate that the left ventricular ejection fraction, so the heart function was stable, that quality of life improved, and that the use of antiarrhythmic drugs decreased during follow-up due to the reduction in ventricular tachycardia. And there were very few side effects related to radiotherapy and only two possibly related effects of grade-three, one case of heart failure and one case of pericarditis. Of course, these are very sick patients that have structural heart disease, so that often have heart failure before treatment. So, this was very encouraging and in 2019, they also presented long-term follow-up data. This is of course very important because at the moment we have almost no experience using these high doses to the heart, which is usually considered organ at risk. So, usually, we're trying to spare the heart as well as possible and here we are delivering single dose of 25 Gy to the heart. So, this is very frightening at first, but also during the long-term follow-up, they could demonstrate that, again, the number of PT episodes was very low, even during long-term follow-up. And that there were very few cases of late toxicity, two cases of pericarditis that were managed conservatively, and then, one case of severe toxicity with a gastropericardial fistula with the treatment area that was located close to the oesophagus and the stomach. This is an overview over the literature. And even though this was just published a few weeks ago, still, there are reports that have not gone into this table. So, at the moment, the field is exploding because a lot of centres are treating patients and are publishing their experience. But still, when you look at the number of patients, these are very low numbers of patients. This again is the prospective trial from Washington University, with 19 patients, this is still the largest experience. And most of these other reports are actually retrospective. In green, I highlighted that many of these case series demonstrated very high-efficacy and very strong reduction of the ventricular tachycardia burden or during follow-up but still, in some of the reports, there were ventricular tachycardia recurrences. In some series here, 8 to 10 patients, had ventricular tachycardia recurrence. And here in this report, all patients eventually had ventricular tachycardia again, and there have also now been reports that not all patients respond to this treatment. So, maybe, the first enthusiasm caused by the initial publication by Cuculich and Robinson has been tempered down a bit. I also highlighted here that the size of the planning target volume has been very different, and with some suggestion that in those case series with higher treatment volume, the efficacy may be lower but still, we don't know a lot at the moment regarding predictors of treatment efficacy. The dose was 25 Gy in almost all of the case series. And what is encouraging is that there were very few side effects actually related to treatment apart from the gastro pericardial fistula that was described in the prospective trial that I mentioned. There's been one other case also of a fistula in a patient also with proximity of the target to the oesophagus. So, this is something that is really critical at the moment. So, how did we get to this point? And now, it's really getting interesting because we don't really know what the method of action is for this treatment. This is a preclinical study that was conducted by Oliver Blanck, who is working with me here in Kiel as a medical physicist. And he did a while back a dose escalation study in many pigs. This was actually done to look at the use of radiotherapy for treatment of atrial fibrillation. And in this dose escalation study, they looked back then on electrophysiology after radiation treatment, but they also looked at histological changes. And what they could demonstrate back then is that with the dose of 25 Gy you achieve some degree of fibrosis, but 25 Gy is not a dose where you would expect fibrosis throughout the whole myocardium. And also, the dynamic of the treatment effect, as I showed you, the reduction of the ventricular tachycardia occurred even during the first one or two months after treatment and there have been reports of very early effects as well during the first days after treatment, which are not explained by fibrosis as a method of action. So, this really questions if fibrosis is the real cause of the treatment effect that we're seeing. And in the past year, there has been a very nice publication also by the group from St. Louis that tried to look at the method of action as well. And what they did is they looked at histological changes in patients that either died after treatment, or that had heart transplant, and they also studied animal models. So, this is kind of bedside-to-bench approach. So, they treated patients, saw significant effect and then, went back into the lab and tried to find out what caused this effect. What they found is that SBRT does not seem to lead to significant fibrosis, there seems to be some kind of fibrosis in the treatment area, however, not as thick and not throughout the whole sickness of the myocardium, as you see it after catheter ablation. And what they could very nicely demonstrate is that radiotherapy with the dose of 25 Gy actually modulates cardiac conduction velocity through increasing protein levels. And this is shown down here, so you can see here, this is doses from 5 to 25 Gy. And this is the QRS complex in the ECG and the cardiac conduction velocity. And you can see here that with doses of 15 to 25 Gy actually the QRS complex shortens and the cardiac conduction velocity increases. And you can also here see that the protein levels for certain sodium channels and connections, so, gap junctions increased. So, fibrosis does not seem, at least the method of early action, and there seem to be effects also with lower doses of 15 to 25 Gy. This is from a recent case report where data from a patient who had received radiotherapy were collected, and he had mapping of the ventricle before stereotactic body radiotherapy, and also, about half a year after stereotactic body radiotherapy. And these are the two images, you can see here that the potentials changed, there seems to be more scar-like tissue here from the electrophysiology standpoint. And you can also see that this happened in a dose-dependent manner. So, these changes were observed in the treatment area that received more than 15 Gy but not in the areas that received less than 15 Gy. So, this seems to be some kind of a threshold for the biological effect. However, other groups have found different changes, they demonstrated myolysis in the myocardium. Also, some changes of apoptosis in the myocardium, at least during the first weeks after treatment, and also, some increase in fibrosis. So, the effect may not be uniform and may also depend on treatment parameters such as dose, and also, on the time from treatment. At this point, I want to, again, encourage you to submit questions that we can discuss after the talk. So, one of the most critical aspects of this, I think, is the definition of the target area. Because again, this is very, very different from what we are used to as radiation oncologists when we are treating tumours. So, I want to highlight some things. So, for visualisation of the substrate for ventricular tachycardia, it's important, of course, to very closely collaborate with cardiology. And actually, the main input for the definition of the target area has to come, of course, from cardiology. And this is usually done by mapping of the ventricular tachycardia that is circulating. Some patients may not tolerate this because they may become hemodynamically unstable when they're in this ventricular tachycardia. So, in some patients, it's not possible to actually map this running VT, but you do only the voltage mapping where you can see the scar area. Then, most patients receive invasive mapping with the catheter, however, as I showed you, it's at least possible to do this noninvasively and the Washington group integrated this on a standard basis into their workflow. However, for many of their patients, they also had information available from previous invasive catheter mapping of the tachycardia. And one of the crucial aspects is how to transfer this information from the cardiology assistance to the actual treatment planning system for radiation oncology, I will address this on the following slide as well. For the planning-CT, of course, that's much more familiar to radiation oncology, we have to account for respiratory motion, so, most centres did 4D-CT or used respiratory gating. A very frequent question is, what to do with cardiac motion? Actually, the degree of cardiac motion and the amplitude of cardiac motion is much less typically than respiratory motion. What we do is we acquire ECG-triggered CT with contrast and account for the systolic and diastolic motion. And you have to keep in mind that typically this arrhythmia arises in areas of the myocardium where there are scar tissues, so, often these are not that mobile, as you would think. And in some instances, you can also see wall thinning in the CT scan. And you may use additional imaging, of course, MRI's not that simple in patients who have an ICD, but if it's possible, you can sometimes detect scar tissue by late enhancement, and there's some discussion whether you may use also nuclear medicine imaging as well. And when we gathered our first experience in our prospective RAVENTA trial in Germany, we did a multicentre study where we had actually images from the catheter mapping and then, asked different centres to point out which area they would treat. And then, we asked them to manually transfer this to the planning CT scan. And what happened is what you see down here, these areas that were chosen based on the same baseline information were hugely different. And also, the transfer from this information that is based on the surface of the endocardium to the CTs imaging is very fraught for failure. And this has also been demonstrated by another group that matched CT scans and data from mapping procedures and demonstrated that there is inaccuracy in the registration of the two parts CT scan and the electro anatomic information. And that there can be shifts of several millimetres and also, huge differences in terms of volume. So, what you can do is you can try to standardise which area you want to treat. There's this 17-segment model from the American Heart Association that you can use to clearly define the treatment area. And then, there are some vast experiences by using, for example, 3D-Slicer, which is an open-source software to bring these types of information together, and to automatically transfer this to the planning CT scan. But this is still in a very early-stage. So, in Germany and Switzerland, we tried to take this experience that exists, and we did a Delphi consensus. So, we tried to establish some baseline consensus, and there were some areas where no consensus could be achieved. This was mainly in terms of patient selection for patients that have advanced heart failure and those, for example, who have prior chest radiation. Then for patients who have ventricular tachycardia that may be coming from different areas in the heart. So, multifocal, you could say from the radiation oncology standpoint the use of particle therapy, that may have advantages in terms of sparing of the normal tissue, and then. the use of the MRI or nuclear medicine techniques. And at the moment, there are quite a few open questions, for example, the patient selections, or whether it's patients with early-stage disease that might benefit or rather this should rather be used in the late-stage setting at the moment. This has only been used in patients who did not respond to drug therapy, ICD placement, and mostly multiple catheter ablations. So, at the moment there are trials which I will also address that are looking at the comparison, actually, of catheter ablation against SBRT. Then, the question of target volume delineation, I think is kind of Achilles heel for this technique. And then, as I mentioned also, the transfer of the target volume to the treatment planning system, here we urgently need validated software solutions that can transfer the whole amount of information. Then, as I said, practically all of the data have been generated by using 25 Gy. However, we actually don't really know if maybe there might be a potential for dose de-escalation because as I demonstrated the electrophysiology effects can also be seen at lower doses. However, it's still not clear whether it might be necessary for the long-term efficacy to actually induce fibrosis and to use higher doses at the centre of the treatment area, by using in homogeneous doses, as we are used to for SBRT, that's still not clear. And then, of course, there are questions of treatment technique, for example, optimal compensation for respiratory and cardiac motion and image guidance. And still, one of the most important questions is long-term safety of this high-dose radiotherapy to the heart. So, this remains a very important topic. At the moment, there are quite a few clinical trials ongoing, mostly in Europe and North America. And as I said, there are now two randomised control trials that are ongoing, that are also looking at the comparison of radiotherapy to catheter ablations. In Europe, there's a consortium, the STOPSTORM Consortium that is funded from the EU, and that is collecting data from many centres throughout Europe, either by patients that have been treated before. So, there's a retrospective registry and also, a prospective validation cohort, and also, work packages relating to quality assurance and also, standardisation of target delineation. So, to conclude, SBRT seems to be highly effective as a salvage treatment in patients with refractory ventricular tachycardia. However, there still seems to be recurrence over longer pause of time. The short-term safety, and this is I think somewhat surprising considering the history of radiotherapy and the heart, is very promising but still, we need more long-term follow-up data. The treatment requires strong collaboration between radiation oncology and electrophysiology or cardiology. And at the moment, we have many unknowns, this is why prospective trials and registry are urgently needed. At the moment, we don't have, practically, don't have experience for other heart rhythm disorders such as atrial fibrillation, so, this is still highly experimental because these patients have a much better prognosis than patients with ventricular arrhythmia. So, I want to thank you for your attention and also e-ESO and Professor Franco for the invitation. And I would like to thank the team here in Kiel and from RAVENTA-trial for the collaboration and the patients that trusted us with this experimental technique.

Prof Franco: Yep, so, thank you very much, David, for the very nicely delivered talk on a very, very intriguing and interesting topic. So, I would open the discussion. So, I would suggest and somehow push the audience eventually for questions or consideration to Dr Krug. So, we will be very happy to process your question and to start the discussion. Otherwise, I will first start with David, so, I think there's a lot of elements for discussion because there is interesting data, intriguing data, growing data, but at the same time, there's a lot of still uncertain points that deserve, of course, investigation and deserve further consideration. So, the first point that we want to discuss is the clinical indication. So, the type of patient where this approach would be feasible, it would be considered indicated. So, first in your experience, would you use it as a standard of care for some specific type of patient, or would you suggest for the person and then, the practitioner, the doctor that would want to introduce that technique in their department to do it only within clinical trial or registries or to, let's say, participate into the consortia that are ongoing? So, is it standard of care or is it only still investigation and do it only in an investigational fashion and setting?

Dr Krug: I think it depends a bit on the clinical scenario. So, I believe that it's a treatment that should preferentially be done in clinical trials. And if you're treating patients, it would be highly recommended to include this into registry so that we can benefit from the experience as a community together. So, there are patients I think, or most of these patients, they don't really have any other options. So, it's a last line treatment for those patients that are not eligible for catheter ablation or that've had ablations before. So, I think you may use it, but I would recommend to either do it within a trial or to refer patients to sites that have a trial ongoing. Because I think at the moment, it's a bit problematic that this technique that it's still in its very early-stages is rapidly spreading and each centre is treating one or two, or five patients and nobody really has a large experience to gain from.

Prof Franco: Sure, that's of course very wise consideration. So, little bit of caution in introducing that into clinical practice, so. And about the line of treatment, so the patient that would be referred to our additional oncology department would be a patient with ventricular tachycardia after attempts to control the arrhythmia with antiarrhythmic drugs, then, implantation of the ICD and then, catheter ablation. So, it will be some sort of end-line of treatment trying to control the disease.

Dr Krug: Yeah exactly, yeah. So, but what is I think is important is that you establish a very close collaboration with the cardiology colleagues as well. So, it's not like the typical maybe oncology referral where we're charged with the whole process from beginning to end that involves the treatment, but here you really need the input of the cardiology colleagues, first, for the patient selection, that's the first thing, and then also for the target volume delineation and also during follow-up. So, this is, I think, very important, you need to have cardiology colleagues that are involved and interested in establishing this. You can't do this on your own, yeah.

Prof Franco: Yeah, so collaboration, of course, with referring physicians. And I would want to address the prescription dose. So, we say, most of, I mean, almost all the experiences were done with single fraction 25 Gy but probably, there's room for changes in the dose, depending, probably, on the establishment of the real mechanism of action of the SBRT in this setting. So, still, only room for single fraction, no room for fractionation here, no sense for fractionation, of course, repeating the treatment into multiple-fraction would somehow make it more complicated to deliver. What's your take on that?

Dr Krug: Yeah, that's a very interesting question. So, at the moment, I'm not aware of any experience using fractionated treatment. So, I guess this is something that would have to be done in a clinical trial, of course. So, what's really interesting is that these patients seem to tolerate the treatment pretty well. So, in terms of acute side effects, there has been some nausea in patients where the target volume is closer to the stomach, for example, but concerning the acute and late toxicity, we have not really encountered any really treatment-related toxicity. So, the question, of course, would be whether fractionated treatment may somehow improve the risk/benefit ratio but at the moment, interestingly, toxicity does not seem the main problem with the exception of patients that have a treatment area that is very close to the stomach or oesophagus; I think that these two cases of fistulas demonstrate that you have to be very, very careful around the GI organs. But apart from that, I think the tolerability seems to be favourable, at least in these very sick patients that have a limited life expectancy. So, for healthier patients, this may be a different topic, and also, as I mentioned for the patients with atrial fibrillation, for example.

Prof Franco: Okay, thank you, thank you, David. And about the target volume definition and delineation, you mentioned, of course, that there's a lot of uncertainties. Part of our information come from imaging, but most come from electrophysiology. So, I'm curious about the process, the information you get from electrophysiology comes in a DICOM RT file extension so that you can easily co-register with our imaging or you need to manually adjust them?

Dr Krug: No. That's the main problem so the format is not, you cannot just import this into the treatment planning system. So, what I briefly showed is that with this open-source software 3D-Slicer, you can import some of the formats from the cardiology systems and you can also import CD data and you can merge these and then, define a structure and then, export the CT with the structure set. There seems to be some kind of a workaround, but it's very difficult to bring these two worlds together, so to say. So, we're at the moment, I think many groups, including our own, are working on software solutions to improve these trends of information, because I think this is really a crucial step in the whole process.

Prof Franco: Yeah, correct, correct. And about organs at risk, I was curious, do you, when you delineate and define a target volume within the heart, then, you would define other heart substructures, say the other parts of the heart, the artery, the other ventricle, the valves, the coronary artery as avoidance structures in order to be taken into account during the optimization process or not?

Dr Krug: Yes, yeah. So, the contouring of the heart is very detailed. Within the STOPSTORM group, there's also a project that is looking at this. The interesting thing is that for many of these substructures, we don't really have actual constraints. So, at the moment we're delineating a lot of structures and collecting these data, we're mostly looking at the dose to the GI organs, to the coronary arteries as well. However, we have, in the discussions with other centres realised that some don't really spare, seem to spare the coronary artery. So, there seems to be some disagreement also on how to handle this. So, this is, I think also an area of large uncertainty and at the moment we're still learning a lot, I guess.

Prof Franco: Okay, okay, thank you, thank you, David. You mentioned briefly about cardiac MRI, and the potential usefulness of this imaging but also, the complication in using that type of approach with patient having an ICD for example, do you think it's a promising approach and there's any role for low-field MRI, maybe?

Dr Krug: I think it's definitely interesting, and you should try to use all the information that you can get, because it's also a way to verify the information from electrophysiology. So, it's given you one more way to make sure that you're at the right treatment site. So, at the moment, we ourselves, we do not really have experience with these MRI. We're working together with our radiology colleagues to establish MRI protocols.

But also, in talking with other centres at the moment, many are not using MRI on a regular basis because it's often a problem with the ICD itself.

Prof Franco: Yeah, yeah, makes sense, that's reasonable. Okay, thank you. And the last question I was curious about, the motion management. You mentioned that the motion is mostly, at least the magnitude of the motion is mostly related to the respiratory movements rather than the heartbeat, the cardiac movements. So, what's your advice and how do you manage motion with 4D-CT and the ITB generation with other approaches, suggest gating during delivery or no?

Dr Krug: So, we have mostly used an ITB approach and also other centres. There are some centres that use gating or even deep inspiration breath hold as well. And we've treated one patient using CyberKnife where we use the ICD lead for tracking, but this is very complicated and the treatment time is pretty long. But some centres, one centre from the Czech Republic that has probably the most experience in Europe is also using CyberKnife. And this is also a question whether these differences in treatment technique matter, and also, if you give the dose of 25 Gy in just maybe 15 or 20 minutes or over one hour. So, it might also be a biological difference in the dose delivery, we're not sure. So, at the moment, we're mostly sticking to the ITB approach. If, of course, we would be getting too close to the stomach, then, we would be using gating.

Prof Franco: Okay, yeah, that makes sense, that makes sense. Okay, so yeah, I don't have any questions so, I will not bother you anymore with my questioning and if not, any question from the audience, I think we can close the session, which was very nice and interesting. So, thank you, David, thank you, Dr Krug, for the nicely delivered talk and thank you, the audience, for attending the session.

Dr Krug: Thank you, very much.

Prof Franco: Have a nice evening.