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e-Session n 537 - 23rd July 2020

The role of MRgRT in pelvic malignancies

Prof Valentini: Shortly. I don't know if you could follow before and I want to report you, what was our experience, namely our talk about the use of innovation technology like the Magnetic Resonance Guided Radiotherapy machine in the treatment of Pelvic Malignancies. Three and a half years ago, when we were under negotiation to get this technology, we tried some brainstorming to set the vision of what could be the implementation of new technology, because when you have a responsibility to be one of the first in Europe in the world, to use a new technology, you need to have an idea of what you would like to take benefit from this technology. So, we framed these three statements that we want to see better, to gate better and to adopt better. And so, after three years, we are here to share with you what we achieved in this a longest time in terms of seeing, gating, adopting. Of course, why do you see better? Because MRI could offer a better resolution, gating better because with the MRI, we could acquire the position of the tumor with this technology through four frames a second. And now with this new release, we can have eight frames a second, so, we can really see. And as I will show you immediately after, also the patients see where the tumor is, it can contribute to positioning the tumor in the right area to be radiated. And finally, to have the possibility to have a fast adopting process today. What were the assumptions at that time? That we could improve soft tissue contrast in terms of guided radiotherapy. We could achieve to have a better vision using no extra-dose for the patient. And as usually, we provide by [Audio Not Clear]. And to deal with the motion management. As I said before, because the patient see the position of the tumor and we could be proactive in positioning it every day, every moment in the right position. And in this way, to minimize the inter-fraction and intra-fraction variation, those were the assumptions. To be consistent with this assumption, we try to identify which one could be the perfect target. There are some publications that we share in terms of the final statement, that the perfect target could be a tumor position and the inside organs that have a similar density of the CT scan. They are highly movable and where we want to provide stereotactic treatment. So, short-course treatment with very high dose, very close to sensitive organs at risky. And looking to have additional knowledge by exploiting MRI technology and possibilities. That's what could identify the best target to position in the patients. That's the presentation, what we manage and all the time. But to be concrete, not to be only with the general vision, we moved to a strategy. So, we try to look if it would be possible to find a solution for complex cases and looking to have a range between the CTV and the PTV, and more large than 95%. So, that the difference between PTV to CPV was very, very small, less than 5% of the overall T volume. And that is what we like to call the strategy of complex key solution. That is a fraction of approach to our patient and the push strategy in the implementation of this technology. Then motion management, that is margin-reduction, and obviously, it is not the way it's tied from what we mentioned before, because, sometime, when we have large volume we have to accept that the ratio could be larger than or 95, but that is away to look for smallest margin as possible in dealing with motion. And finally, to have a clinical decision support benefit from advanced managing analysis and to the different MRI technologies and with addition

radiomics. MRI only workflow means to avoid, to have the CT scan, but that is really a research project that we're implementing in the last month. One stop, one shot to be fast and to be consistent, to have only one technology that could cover all the different steps of the treatment. So, that's what are the strategies that we implemented. With this key perspective, we will go to the tumor of the pelvic to go to see what would be possible to manage. Of course, focusing on this perspective, we implemented different trials, more than 25 trials and we have already collected the publications. They're publications that are sometime targeting a complex case solution. You see seven publications because there's a possibility as a proof of concept that this technology could allow to overcome some issues in the daily practice. And other publications, they are in some way, fostering the following larger and cooperative research. Actually, we're really moving now in terms of the ongoing research in the phase two and collaborative large phase two study. So, that is a typical, when you are going to implement a new technology, that you have an evolution of the knowledge and these evolutions sometime are for showing a single-case solution, sometime to fostering a generic or to new hypothesis study. And now, we're in the piece of larger phase two and phase three randomized trial. So, if this is the vision and the strategy that we put in place in the last two years and starting the acquisition of this new technology, inside our department, where we have other equipment, but this MRI-guided represents, for sure, a stronger innovation, respected, traditional patient management. Now, we go to see what we can say to you in a GI, GU and some other generating hypotheses treatment a year. For rectal cancer, there was a publication, years ago, where we review what would be the early publication and benefit that we could find in the literature about the early use of the Magnetic Resonance Guided Radiotherapy. And you can see that there's a clear possibility to look for escalation of the dose, even with the sternum being on the GTV, that the tumor because it's visible and trackable, and to reduce the margins for the inside capacity of the technology. And then exploiting some features of the MRI, for looking at the possibility to give variables. And this was exactly the first experience, you see that when we explored the use of the possibility to give a concomitant booster to the blockade tumor, how it was visible every day. For us the blockade tumor, as well, also was visible, the shrinkage of the tumor also for the patient, that was really very pleasant motion for the patient to see that the long treatment, the long fight, weeks up to treatment, it wouldn't be possible to really see for the patient reduction of the blockade tumor. And we explain of course later to the patient that that was really something that was also important for the patient perspective. And so, we could have a reduction of GTV, and we could really and safely, with very low toxicity, give a full dose and we got a quite very stimulating PCR in the first group of patients that we treated. And for bio-boosting there are data that are exploring, seminating hypothesis trials, the possibility to tailor the dose inside the body, to looking at the risk-factor that we can collect from the DWI or as we will show soon by radiomics. Having the possibility to collect such a large extension of MRI imaging along the treatment, the possibility to look, if it's possible to add predictors of response, was quite attractive in our early experiences. We said before that was one of our strategy goals to personalize treatment and exploiting advance imaging, and we saw that, by selecting three features, it wouldn't be possible to have a cut-off, where over this bar, patients didn't get the pathological complete response. We were lower than with these radiomics features to the respect to the bar. There was a higher chance that it was fully a pathological complete response in all cases. And with this background, now we launch a phase two trial where we put multi parametric excess, before the beginning of the treatment, after two weeks of the treatment where we still confirmed the data that in that moment Radiomic feature in the bio markers, that we could collect and another possibility to predict the achievement of a PCR and, you know that, it is already reported in some other publications. And among these delta values, to tailor possible different scenario to reach no surgical approach in a possible intensification of the treatment or escalating the dose and the surgical procedure in very area, because the data are identifying a very poor responsive patient. So, this is what we try to call, theranostic approaches for Rectal cancer. And now, I stop because there's a reminder for the participants, if you want to add some questions or disapprove this first part of rectal cancer and the production, you can put questions and then I hand my presentation to Professor Francesco Franco, he will forward them in opening the discussion. So, that is for GI, namely for rectal cancer, the possibility to increase the dose and to tailor the treatment, according to their response. Taking benefit

from the bio boosting or bio data that we can call that GU. And GU, we have a patient that what could happen along the treatment for cervical cancer, because it's very well-established possibility to see it, to know that there's a modification in the position of the different organs along the treatment, by the shrinkage of the primary cervical tumor. And what we observed, that was really important in this situation is the position of small bowel. Because, as sometimes it's possible to observe, there's a group of women where the small bowel can go very down to the patient. And that is the typical situation or what we call complex cases solution. And you see that in this lady, we have a small bowel, very deep into the Douglas sack. And we saw that this small bowel became thickened and still, if the lady didn't have a clear sign of diarrhea, we immediately re-planned the treatment and we could, in this way, avoid the possibility to have higher impairment of the small bowel. And the possibility was sorry, was quite, as you can see, tangible because the small bowel thickness took the same shape and the same intensity of the not-radiated small bowel, instead, at the beginning, it became thickened. So, we concentrated to the individual anatomy, this complex case could be managed quite simply. And the very early outcome that I said were really helpful for generating hypothesis of following study. We observed that after diarrhea, respect a similar patient that we radiated by traditional machine accelerator, and less urinary issues in this group of patients. Very early, very generating hypothesis idea, but having the possibility to track also the whole volume in such a precise way, easier than from a CT scan. We invigorated that radiomic features with the measurement of the volume because there are data that obviously put in correlation the volume of the tumor and the possibility of the control. And having the bar-level over the possibility to get optimal outcome is very reduced. And we combined this volume algorithm with radiomics. And just go with the same framework that I tried to explain before to tailor for the treatment. And also, to integrate the possibility for additional dose contributions accordingly to prediction that we can collect, monitoring the volume, monitoring the MRI and the diffusion with images and also the possibility to collect the radiomics. That was a very preliminary flavor, what we are observing for cervical cancer. Any question please, use the system. Prostate. Prostate is another domain of interest. There are publications by the Amsterdam group, where a quite large number of patients will receive a quite fraction Magnetic Resonance guided and with test and assumption, and then the validation that it would be really possible to observe the target in this way to reduce the margins. With all the possibility to add daily re-planning and optimizing those, and also reducing toxicity. That was also something that you can really perceive, as easy to manage, in some way, at the end of the story, because without any fiducials, and with higher possibility to manage these cases, sometimes also put a stop at these cases, some complex situations where we can really see the idea that it's possible to focus the dose in a very safe and a very precise way. Data are consistent, it is a very crowded table, but it is showing that it's consistent, that the benefit in terms of quality of life still remains stable even after one year of short-course of the stereotactic procedure high dose MRI-guided for prostate. We're testing something that is, I think, very challenging for any Radiation Oncologist in prostate cancer. That is the issue of recurrence and so the issue of re-irradiation, and now we start to exploit this possibility to see, and to show there's recurrence area inside a re-irradiated pelvic into a daily monitoring. In this way, look at the possibility to have a re-treatment with high dose, and, as you can see, with very limited acute toxicity, and even of course with very limited follow-up, because this treatment started the one half a year ago. But the solution that we could, in some ways, expecting to reach for these patients could have a real impact because, you know, very often the surgeon says to the patients that they go to surgery immediately, they will not lose the possibility of recovery by radiation therapy in case of a relapse or recurrence. And then that is not doable to have vice-versa. So, if the patient receive radiotherapy, they can't have surgery afterwards, so, they lose it the possibility of second shot. And that is one reason that this discussion is proposed by urologist to the patient. And then, if we could provide, of course, in a specialized center with this technology, a possibility to re-irradiate quite almost radically this recurrence, we will weaken this argument that sometime is used in the discussion if we want to offer radiotherapy or surgery for prostate cancer. And finally, we have also try, and that is another complex case solution, 94 year old man with very many, many complexities, so the possibility to have partial bladder irradiation, that with this technology would be doable and in some way successful, because we could control for 18 months, they grow the tumor for a patient that could not have surgery, could

not have any other technicality without producing any great irradiated bladder symptoms, because we only were very collimated and we didn't suffer with urothelial for many, many months. And that there's a reminder for questions for these other generating hypothesis proposals. Finally, in this perspective where we approach also something that is not so usual to be irradiated confident of this capacity to have a high possibility to see the target, to put the dose precisely on the target, the controlling, the movement of the patient. We went to irradiate abdominal node. And that is part of the history where many cancers, ovarian cancer, but sometimes also Neuroendocrine cancer, sometime also colon cancer, where a patient responds in many sites to systemic chemotherapy, but some isolated nodes remain in the abdomen. And they're very moveable, very, very moveable. And the possibility to see them, the possibility to provide high dose to them, and taking care of the position of the small bowel that is around it, and then the re-planning every day this patient and everything is delivered in one hour and one hour and 10 minutes, that is the usual average time for this full adaptive gated treatment is really quite attractive, because we collected evidences in first cases that it's possible to keep the level of the dose to the bowel inside the typical constrains limiting the volume of the irradiated amount of bowel over, that is considerate at risk for side effects. And reaching what we want to reach, that is to provide a ratio of 0.95 in the most of our daily treatment. So, at the end of this sharing with you that the innovation of technology takes time to be validated in terms of providing real data around the assumption that we have that this technology could represent the real benefit in the daily life. So, promising clinical results. And as I said, we could then go towards phase-two study, some collaborative study to move from a first definition of the better benefit of the better employment of this technology, to keep always the benefit to a complex cases solution, to move, to provide more robust evidences of the benefit of this technology. Of course, selecting the proper patient for the use, I am not saying, as I will show you immediately, that, that is not the technology for any treatment. Of course, we have to consider that this machine is quite costly, this machine takes time. And the volume of the patient that we can treat with this machine is not reaching the 20 patients a day, maximum. And so is not a high volume, but if we have a proper number of good Linear accelerator, we have a large number of patients. We have patients that could have a real benefit having such a machine in the pipeline of the technology of anybody in the center. And that approach is really successfully performed, and we have an impact and the capacity of preventing toxicity during the treatment, as we show in the cases of the cervical cancer. And probably there are new clinical indications this abdominal node is one of them, recurrence in the irradiated prostate cancer. There are some other ones that these are deeper exploration. So, in some way, when we had a debate few months ago, with MRI guidance replace CBCT, we discussed that probably no for all patients. But there will be, there will be a situation as we described before, that could have a benefit in terms of being addressed to MRI guidance treatment. And also, when you need to reduce the IGRT dose, it could be another benefit using MRI. These are the key messages of the new technology, that I was really glad and honored to have this possibility to share with you, of course, any time that you have a new technology you need to do at the very committed group of people with different commitments. I'm delighted to have such a standing group of colleagues that are working around this treatment modality. Thank you very much for your attention. And now I leave to Francesco comments and questions, if you would like to do.

Prof Franco: Thank you. Thank you very much, Professor Valentini for this very, very interesting educational and clear talk about this new technology. So, actually I don't see questions coming from the audience. So, I invite all the participants to come up with questions if needed. And so, Professor Valentini will be more than happy to receive your questions. Otherwise, I will start in opening up a bit of the discussion. I was kind of intrigued by some of the statements you made. You pointed out that MRI Guided Radiotherapy is basically a changing paradigm compared to the usual way we see radiotherapy. You have a new imaging modality, completely different from what we as radiation oncologists are used to work with. Normally, we're more exposed to CT much easy than MRI. You have a different adaptive approach and online adaptive approach. And you have also the chance to tracking the tumor, so, you have the gating. So, you have different aspects which comes together in a single volt machine. And the management of all these different tools requires

expertise, require experience, requires organization. And probably it is a change in the normal workflow of our radiotherapy department. So, since you have a long-lasting experience with MR was intriguing, interesting to know, how did you manage to provide all the different professional radiation oncologist, medical physicists, RTTs with the expertise needed to implement this technology? And how did you make it doable for Radiation Oncology Departments? So, that might be a challenge for our center that wanted to implement and start with this new technique.

Prof Valentini: Yeah, of course it was a really great challenge because we were the second machine in Europe and so, we could not have the experience nearby. Of course, there were some escalations in USA, so, some of our staff, physicists, radiation oncologists and RTTs went to USA for a couple of months to take the benefit to be in an environment. And they needed also to be trained in the reading MRI image, because it is a different technique. I'm to be honest that we already have some training process because with the fusion that we do quite often in the pelvic, mainly for prostate, by MRI and CT scan, in the designation and planning, already we have in place training for reading, for understanding MRI. But nevertheless, we have also, the need sometimes to have a good collaboration with the radiologist for the proper use of MRI. On top of this process that was managed before, we also wanted to, as you said, very properly to think that this machine needed a completely different approach. So, it's very nice to see that physicists, the technician and the radiation oncologists, are in the same room together for the wool sheep they have. And so, it means that they really work completely together. It'll require also a different flow track in terms of simulation time. Because, of course, some simulation time has to maybe manage it in some parts of the day. And not in a different room, because we do CT scan in our simulation room, but then the simulation has to be repeated a couple of times with the MRI. And so, you're required to find a proper slope and also to manage all the control for the QA of the machine of the planning. So, it's really a completely different approach, but at the end of the story is doable. If you want to achieve a successful program and that is really the key message after three years. Because we started with the common unit that had some characteristic features that were peculiar of that machine, that it was a very stable machine, very, very, very reliable machine. And then we move in a Linac accelerator, very nicely in terms of possibility of optimizing the dose but sometime, have some more complexity, not so much, but we have to deal with some technical more complexity there. But both these two aspects were successfully managed, because we want to achieve a real implementation in the daily life of the department, this technology. So, it's not trivial, if you want to go there, you need to plan good training to open mind to change the framework. And nowadays there are in Europe around 10, 12 installations to go to see a couple of centers to find the best practices. to translate it in your own hospital.

Prof Franco: Thank you. Thank you very much. So, I take the chance of one of the points that you touch upon about the difference between the two releases of the system, the Cobalt 1 and the Linac 1. There's a question coming from Qureshi from Pakistan, asking whether you experienced clinical differences in terms of toxicity, for example, the toxicity in rectal cancer, for patients treated with Cobalt compare to Linac, for example, taking into account of the different penumbra that the Cobalt has, or the different technical characteristics.

Prof Valentini: Yeah, we manage around 40, right now around 50 cancer patients, 50, 52. The first patients who had the Cobalt treatment they had a higher incidence of grade three diarrhea. That was true. We personalize the treatment, but in some of them there was a slightly higher possibility. And we could not treat all the patients when the patient was very weak. It was that the dose will not be optimal for prostate or for cervical cancer. So, to have the Linac was really something that overcome this limitation for sure. Of course, we have to take into consideration that we have a machine we thought to be Tesla. So, with very low fuel. And it allows us to do gating daily, because 8 frames a second is really something that changed the life. The patient has a screen that allows him to see his own tumor, and this can control the positioning namely for after abdomen of the tumor inside the target volume. That is really doable with those 3 Tesla. And also 3 Tesla interfere very slightly with the dose distribution. So, that for us was really a tangible benefit when we moved from Cobalt to Linac accelerator. Of course, Linac accelerator usually, as any Linac accelerate has a

sound complexity, sometime of down-work and then we move, as I said, very, very stable. We had a 98.5% of treatment time with Cobalt and now we are at 94. something with Linac accelerator. So, we decreased a 4% of treatment time without having the Cobalt, but the Linac accelerator. That is quite usual and obviously with a new machine it's something that anyway is still accessible, so, we didn't suffer a lot from that change. We were very glad we've moved this way.

Prof Franco: So, actually you're enjoying the advantages of having the Linac version and being able to cope with—

Prof Valentini: Absolutely.

Prof Franco: with the technical complexities. So, I was also interested in knowing your opinion about the way to perceive the MR Linac-base treatment. So, do you this type of treatment more suitable for stereotactic treatment, let's say a higher hypo-fractionated treatment on smaller volumes? Or do you think it's also suitable for conventionally fractionated treatment on larger volumes or probably it's a versatile type of machine that can do both? So, how do you see the correct clinical setting of this type of machine in treatments?

Prof Valentini: Of course, the future is namely for treatment of small volume with stereotactic approach, namely where the upper abdominal and sometime also in the lung, because we did some studies out of the focus of today, but after when you have more than seven CM in the movement of the lesion in terms of the ETV. It was really showed that the MRI system is superior to cover the tumor than traditional combined or ??voltage?? system. So, for sure, in the moveable organs this would be a really tremendous benefit, because it is not invasive for the patient, no Fiducials at all and you can really easily manage this situation. For the tumors, where you have to give a dose, that is also as I show you in the pelvic, there's also a rationale for the larger volume where don't you need to do a dose. I don't think it will be really helpful outside some special case where you have, as I tried to show you, a very strange position a small bowel and so on. But otherwise, if you do only large volumes, no, but if you give large volume, and we want to escalate a dose of the primary and that will allow you, really, not to provide additional dose to the organs at risk that you already involved in the large volume. So that is still a possibility.

Prof Franco: So, advantages come in—

Prof Valentini: No, no. Yes, yes.

Prof Franco: From the delivery and from the imaging system as well together with the gating, together with the online adaptive possibility that all together will be able to enlarge the therapeutic window for—

Prof Valentini: Correct.

Prof Franco: Okay. Thank you. And I was also interested in knowing about the chance. I think you mentioned slightly about that to get rid of the CT for simulation and starting with MR base on the simulation and dose calculation on MR, is it feasible or not yet? It's still investigational?

Prof Valentini: Yeah, of course it's investigational but the first data are very, very attractive. As we do a synthetic CT, it will be really intriguing to see that this synthetic CT moving from MRI and planning of synthetic CT you have around 1% difference in the dose distribution in terms of BBH, respect what article that the dose distribution from the original CT scan. So, we did a CT scan, we did MRI, we did synthetic CT from MRI and comparing the plan from original CT and the plan from synthetic CT, there was around 1% of dose distribution difference. If not nothing, but it means that it's interesting to invest, to optimize it for the algorithm, but accept it could be doable.

Prof Franco: So, it's something that theoretically can be doable, it's reliable and probably in the future that could be implemented in the practice?

Prof Valentini: Yeah.

Prof Franco: Probably.

Prof Valentini: It seem, it seems, of course, as I said, it's quite experimental but there are very good, very good message and positive messages.

Prof Franco: So, thank you. Thank you very much. I think now it's 7:05, so, I think we should stop the session. So, I want to thank Professor Valentini for the very, very nice talk and interesting topic. And all the participants for the participation. So, thank you everyone, and have a good night.

Prof Valentini: Thank you. And hello to everybody.