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Radiotherapy for prostate cancer: an historical narrative review

Dr Bossi: Well, thank you, thank you very much to give me the opportunity to share with you some insight about the history of radiotherapy, but I guess also about the future of radiotherapy. These are a few disclosures of mine, which will not impact the main message I will try to give you tonight. And as I told you, I will also try to give you some insight and not only the history perspective of radiotherapy for prostate cancer. But let me first start with this very interesting slide that I took from Anthony Zietman that you certainly all know. He says here that the arrow of progress is not necessarily a one going from less technological sophistication to more and more technological sophistication. You may also find out that at the end of the day, in terms of cost and time, you may have this sort of curve telling you that sophistication in medicine may not always have this arrow that you can see on the left-hand side. So said, let's go back to the past when I started doing radiotherapy for prostate cancer, and this is for sure hard to believe for some of our listeners tonight, this was the kind of exercise that we were doing. You see here some bone anatomy of the pelvis, and these are the fields that have been used to treat prostate cancer when this was born. These were very primitive ideas about the prostate, the location of the prostate in the anatomy of the man. You can see here on the right-hand side, that we may have used also some sort of contrast media to better identify the apex of the prostate. This is how prostate radiotherapy started, and these are the kinds of dose distribution that we may have had at our disposition at that time. You can clearly see here that this was very primitive, it was a dose distribution based on 2D, two-dimensional images, like the one on your left-hand side. Nowadays, a big advancement came from the possibility to both use CT images and MRI in a fusion in order to get a better view of the anatomy of the prostate. You can see here, one of the first papers that dates back to the end of last century, in which both source images, CT scan and MRI, were used to better define the anatomy of the prostate. And nowadays, this is what we are systematically doing when we want to irradiate a prostate cancer. And this is particularly useful, especially, in some aspects of the gland. You can see here that the comparison of what you see by CT scan on the left-hand side and what you see by MRI, certainly favours MRI view, and especially this is true in the apex of the gland. So, nowadays, CT is used in conjunction with MRI for treatment planning of external beam radiotherapy. But certainly, another extremely important advancement in the technique of irradiating prostate cancer is the multileaf collimator. Nowadays, multileaf collimators have been used to exactly define and target the volume of the prostate and eventually the seminal vesicle and to better spare rectum and bladder, as you can see here in this example. And this may be applied for the number of fields you are using to treat external beam radiotherapy of prostate and what you have and what you get is this sort of very precise identification of the target, and especially what we call Intensity Modulated Irradiation. As you can see here in IMRT planning, which is now the up-to-date technology we are using to irradiate prostate in the external beam radiotherapy world may obtain this sort of dose distribution. The rendering here by colour wash is particularly interesting because immediately gives you the idea that the red zones are the ones taking a lot of dose, while the blue zones are the ones which are almost not-treated. And

so you can see here that the dose is quite conveniently concentrated into the prostate and the base of the seminal vesicle for this particular patient. This is what I call Intensity Modulated Radiotherapy, up-to-date technology in 2022 to irradiate the prostate. But people which are nowadays irradiating the prostate by external beam radiotherapy have also to face a second problem, not only the definition of the target is challenging, but you also have to acknowledge that during the course of external beam radiotherapy treatment, that may last several weeks, the prostate is not always in the same position. So, the organ motion is something that we have been learning, should be tackled in our preparation of the treatment. You can see here a very interesting experience of Renaud De Crevoisier, published also some 10 years ago in which the same volume of the prostate could be identified on several CT scans that were done during the treatment of a single patient. And you see here that the prostate is not always in the same position because of the volume of the bladder, and, of course, also because of the volume of the rectum. And this translates of course to the need of clearly identifying session procession, the volume that you have to irradiate. You can see here, as I told you, that clearly the rectal volume during IMRT and the bladder volume during RT may change, you see here a few patients on the left and right side of my slide in which rectal volumes have been carefully calculated during the treatment times in days and you see here that the variability is quite important. We know now that rectal volume may during the treatment increase the volume and bladder, as you can see here on the right-hand side, may decrease the volume. So, at the end of the day, you want a technology that we call image guidance technologies in order to better identify the prostate during the treatment. And indeed, you see here that a list of technologies had been proposed. And the first one here, skin marks with weakly portals, it's hard to believe today, but this is the technology I was using when I started irradiating prostate cancer. It's a baseline technology, which of course does not take into account the movement of the prostate. Nowadays, you can see here that most of those technologies are using planted markers in the prostate, that gives you day-by-day the position of the gland before every session of radiotherapy and probably the best solution is the last one you can see here, which is the real-time in-room MRI. And believe me, this has totally changed, it's something which came to the market very recently, but this has totally changed the landscape of the external beam radiotherapy for prostate cancer, because nowadays you have the possibility to use MRI images every day in order to better target your prostate. And as you certainly know, MRI images are much more precise as compared to CT images in order to define the target. And indeed, we have now vendors that propose this sort of machine in which they couple from one side an MRI, a 1.5 Tesla MRI scanner, which a linear accelerator, which can treat the patients once an MRI has been obtained. And believe me, this is probably, in 2022, the best technique we have in order to take advantage of imaging to better treat our patient. But let's integrate all this in the site of the future, what will the future, in my opinion, give us in terms of technology for the treatment of prostate cancer. And I have here at least four bull-points that I would like to discuss with you. The first one is the better use of established technologies. The second one is the spread of new technologies. Third point that I want to discuss, the answers to all questions, and finally, what I mean by patient-centred approach. So, better use of established technologists. This is a cartoon which is taken from an old paper of a friend of mine, [\[Audio Not Clear\]](#). Now, in which the idea of boosting a dominant intra-prostatic lesion was proposed. You see here that the concept is to define on the left-hand side an intra-prostatic lesion, which is the dominant, in terms of prognosis of the patient, lesion into the prostate. And on the right-hand side, you see that we may obtain a dose distribution which is centred on this dominant intra-prostatic lesion. This was something that was proposed years ago, but nowadays, we have the first randomised trial, which has been published very recently, the Flame Trial. And this idea has been a challenge versus the standard treatment. You see here the JCO publication of 2021, and the Flame Trial is a Dutch and Belgian trial. You see that patient, mainly in the high-risk group, 84% of those patients, have been randomised in a standard 77 Gy in 35 fraction-treatment versus a same 77 Gy for the whole prostate with a boost specifically on the dominant intra-prostatic lesion defined on multi-parametric MRI. And indeed, two kinds of conclusions from the Flame Trial. The first one, that is really, and this is something that we suspected from years, a very clear dose response in the gross target volume defined on multi-parametric MRI. The more dose you can give in the dominant intra-prostatic lesion, the less likely is the patient to experience a PSA

relapse during this follow-up. But the second conclusion is probably even more important for the prognosis of our patients. And you can see here in this cartoon, there is both in terms of local failure-free survival, and in terms of regional and distant metastasis-free survival, a clear advantage with a hazard ratio of .33 and .58, favouring this strategy of boost in the dominant intra-prostatic lesion. And this has just been published early this year but Groen. So, this seems to tell us that probably this is the way to go. We have the technology to do this, in the near future if we can apply this technology, we may really get better results to our population of patients. And of course, this kind of patient is probably the best patient profile for such a strategy. He has no cancer on the left lobe of the prostate, he has 9-millimetre of a ISUP 3 cancer on the right lobe. And it's easy to figure out that this can be easily targeted by this technology. Probably a patient like this one with a bilateral cancer, 21-millimetre on the left lobe, 9-millimetre on the right lobe, it's something that you may not treat in this way because of the multi-focality of the disease. And so, my conclusion is that, yes, this is certainly a nice technology, but probably it's not a one-fits-all technology. We have something different, something more. And this something different, something more that we may offer to our patients comes from this consideration. Look at this gentleman, this gentleman has a T3b cancer with a clear infiltration of the right seminal vesicle here, a very bulky disease outside the capsule and an ISUP 4 cancer. A very locally advanced, very high-risk prostate cancer, which is the technology that may help you in better treat these patients? Well, as you probably know, I am a fan of brachytherapy, and probably you can see here that my needles that are put into the prostate, implanting the prostate from the apex to the base of the gland may clearly be put also in the right volume, which is the volume of the seminal vesicles. So, high-dose rate brachytherapy may help to better treat the disease for this patient. And this, I think it's a very established technology, but something that we may want to develop in the near future for patients having very aggressive disease. And the use of a brachytherapy boost very recently has been challenged by Kishan in a Jama Oncology paper and what Kishan has done is a very clever exercise because he has tried to identify the interplay between hormonal duration and use of a brachytherapy boost for very high-risk prostate cancer. And as you can see in this panel, on the left-hand side, you have the androgen deprivation therapy duration, which is needed in order to get the best result if you only use external beam radiation therapy alone. And this ADT length should be of 26 months, but look on the right-hand side, as soon as you use a brachytherapy boost for the same patients' group, the need you have in terms of androgen deprivation therapy length goes down to 12 months and you got the same results. So, this also tells us that this technology at least may translate in less testosterone decreasing needs for our patients. And this is something that we may have to consider in the near future when treating prostate cancer patients. But of course, brachytherapy is not for all patients, if you have big prostate, this is not a good solution. If you have big RQP defect, as it's the case of the right-hand side, brachytherapy cannot be performed. So again, we are here facing a strategy which cannot fit all our patients. Which is another strategy that has been developed recently and, in my opinion, has a great future in the treatment of prostate cancer? What I call the spread of new technologies. And I refer here to Anders Widmak's study, which is a randomised study that you certainly know, it's a Scandinavian trial that has compared the conventional fractionation in the treatment of intermediate and high-risk prostate cancer with an ultra-hypofractionated regimen. Patients here were treated on SBRT in only 7 fraction of 6.1 Gy. This was a non-inferiority trial. And you see that the technology that was used really makes use of implanted fiducial markers, as if this is the real technology you need if you want to drop your total treatment time for 39 to 7 fractions only, and you're certainly aware that the results were compatible in the two populations of patients clearly showing that there is not a detrimental effect if you opt for a hypofractionated regimen, both in terms of the primary endpoint, the failure-free survival and the secondary endpoint, the survival probability of the whole population. And even in terms of patient reported outcomes, you see here that there is almost no difference in the long-run in terms of bladder, gastrointestinal and sexual toxicity. And this I think is very reassuring for our patients and their families. Another aspect that I think will change our way of treating prostate cancer is the POP radiotherapy trial published last year by Murthy and Al. You know that the idea of treating or not the whole pelvis, at least in very advanced disease has been debated in the literature for years. And finally, we may have some nice answers by this Indian trial. Not a

very big group of patients, 224 patients that have been randomised to a prostate-only radiotherapy, 112, or a wound-pelvic radiotherapy. And you see that patients were identified by the Mack Roach formula. They were whole high-Gleason patients, mostly, and the treatment they got was totally acceptable by modern strategies. Biochemical failure-free survival at five years was the principal endpoint of the study. And you probably know that you can see here on the right-hand side, that the endpoint was clearly favouring a wound-pelvic radiotherapy for those high-risk patients in a post hoc analysis, also distant metastasis-free survival was favoured by the radiation of the pelvic lymph nodes. And you know that metastasis-free survival is a much more solid endpoint as compared to biochemical failure-free survival. Indeed, indeed, doing wound-pelvic radiotherapy translated in less regional pelvic nodes recurrence. And this is exactly what we are expecting when we treat pelvic nodes. So, this, if you need, this is something that confirms that pelvic radiotherapy is really important. Again, in terms of patient reported quality-of-life outcomes, no difference in the long-run for the two groups of patients and this is also reassuring for our patients. Why did Murthy find such brilliant results? Well, probably my bias is that probably the fact of clearly identify the population of patients to irradiate was the key-factor. You see a Roach formula, more than 20, but also, the systematic use of PSMA PET, 80% of patients, used that. And indeed, if you try to identify the patient that may benefit for a wound-pelvic radiotherapy, you need, one side, the Roach formula that will rule out patients having a very low livelihood of having metastasis in the lymph node. But on the other side, you also want something else, PSMA in this case, ruling out patients having already metastatic disease. So, Murthy has clearly identified the window of curability for wound-pelvic radiotherapy. But again, this shows that wound-pelvic radiotherapy cannot be a one-fits-all technology, you need to select your patients for it. And the last point I want to make is patient-centred approach. We don't have to forget that patients should be the centre of our studies and of our efforts. And it's quite interesting and I guess this should be known by everybody that very recently again on the Red Journal, there was this meta-analysis showing that, suggesting to patients to have physical exercise during radiotherapy may translate in, at least in terms of urinary toxicity, in less urinary toxicity for our patients. So, we may talk about technology as I try to do today, but don't forget that very simple suggestions like exercise during radiotherapy may per se translate in less side effects to our patients. And this I think it's a big conclusion that should never be forgotten by our young colleagues. So, what is my conclusion for the future of radiotherapy of prostate cancer? Focal, multi-parametric MRI-guided boost will certainly have to be implemented. Don't forget that brachytherapy may also has a role for high-risk disease as a boost together with external beam radiotherapy, extreme hypofractionation for a fraction of patients is certainly the way to go. And pelvic nodes irradiation should probably also be standard at least for a very good selected group of patients. But at the end of the day, what I think is that we don't have to forget that the centre of our efforts should be the patient. And as I told you, sometimes, you just need to give patients very simple suggestions, like do exercise during radiotherapy to have less side effects out of their treatment. So, I thank you for your attention and Dino, I guess, this was my last line.

Dr De Bari: Thank you, Alberto. Thank you very much for your brilliant presentation. It's not a surprise for me, but it's always a pleasure to listen to your lesson on prostate cancer. For the instance, there are no questions from the audience, waiting for them, I would make just a comment, but I'm really interested in knowing what do you think. When you look at the data about the Flame trial, these data are clearly interesting, because they showed that we should increase the dose, if I'm not wrong, there are no so much people that are treated on the pelvis in this trial.

Dr Bossi: Correct, yeah.

Dr De Bari: Okay, when we look at the patient's characteristics, a lot of these patients are high-risk patients.

Dr Bossi: Correct.

Dr De Bari: The staging procedures were not the same of the POP RT trial, but in any case, we can see that looking at these two studies, it seems to me that the same patient could be treated with or without a boost, with or without pelvis, with or without have a fractionation.

Dr Bossi: Yeah, this is a very intelligent point.

Dr De Bari: And if we had the data from the Nordic trial that you showed us on SBRT, there were patients with mid. High-risk features.

Dr Bossi: Correct.

Dr De Bari: I'm completely aware about the fact that we cannot compare the results of studies of patients treated in different studies. I'm completely aware and I know that from a methodological point of view is not correct, but finally, in our general practise, what we look at are the, you can say, the course of a study, okay? And looking at the course of these three trials, it seems to me that there are not major differences justifying one approach over another one. Probably, the progression-free survival of the POP trial is in the arm of patients treated, in the group of patients treated with pelvis, probably, this group has better results. But as you said, the staging in this trial was really, really, really careful. So, there is a major selection in order to arrive to these results. I'm not sure that for clinical reasons, for logistic reasons, for national reasons that this kind of results can be reproduced everywhere. I had the chance of working in Switzerland, where we have a quite good access to PET PSMA. Recently, when I say recently it's 2021, the insurances reimburse the PET PSMA, the PSMA PET also in the staging of high-risk patients and not only in the context of biochemical relapse, like in France, for example.

Dr Bossi: Yeah.

Dr De Bari: So, to consider that the results of the POP RT trial are the same that could be obtained everywhere, I'm not so sure. Again, I think that it's, and I completely agree with you that the POP RT trial was the trial that we need because the five trials on pelvis irradiation were all negative, but everybody knows the limits of... methodological limits and staging limits that characterise this trial. So, that for sure that the POP RT trial was the trial we need. But if we exclude this ideal world, probably these results will not be exactly the same. So, when we go in the real-life, probably, the Flame trial and the POP RT trial with or without pelvis, are we sure that are so different? You know that in France I think that there are, when I left France in 2020, there were only two centres that could make the PSMA PET in France.

Dr Bossi: Yeah.

Dr De Bari: All over, in France. So, in the real-world, how to decide, finally, it's easy to decide for me not to perform HDR, I'm completely convinced about the benefit of HDR drug therapy, but I don't perform that in my department and in Switzerland there is only one centre delivering brachytherapy and only as exclusive treatment and not as a booster despite the evidence. So, as you can see, it's easy sometimes to make choices. But when we look at some other situation it's more difficult. What do you do in the real-life for a patient with high-risk, a patient that could receive the Flame or the POP RT strategy? How do you decide? Sorry for the long comment, but it was needed for my point of view to give a background.

Dr Bossi: No, sure, sure, and your point is very well taken. I'm totally aware of what you said and there is for sure a lot of truth in what you say, as you mentioned in France, for example, we still have a lot of difficulties to get PSMA scan, not only for high-risk patients, but also in the relapsing ones, so, we are really in a... But what I wanted to give was a little bit of this idea, because you also know very well that the field of radiation oncology for prostate cancer in the world has a lot of debates going on. There are people which are convinced of the need of a brachytherapy boost, and then, there are editorials of others radiation oncologists saying, "No, no, this is not the way to go." Well, my bias here, my idea here, Dino, is that we, as radiation oncologists, we have several different technologies that we may apply for the patients we have in front of us. Correct,

you may not give HDR boost to your patients because you cannot give it, but you know that probably if you can give 7 fraction of SBRT, you are still giving a good treatment to your patients because you have technologies which have been challenged by the Scandinavian Trial, which you could use in your daily practise to inform your treatment. So, I don't feel the need in the radiotherapy world, you know, to those battles, intestine battles; we should really think in terms of different options we may have to offer to a single patient. And really what I do in my clinical practise if I see a young patient with a very bulky disease, I really think that a HDR brachytherapy may help him a lot. You also know that very recently systemic therapy for those patients has totally changed with the addition of two years of abiraterone for those patients. So, it's a moving situation in which we have to be aware every day more. What I say to my colleagues, the surgeons, is this, you just have a knife in your hand to do radical prostatectomy. We have several kinds of different technologies that we may better adapt to our patients. And this, I think, is something the radiotherapy community should know. I don't know if it was an answer to your question, but it was a common on this topic that you have raised, which is a totally correct one.

Dr De Bari: I don't think that there is only one answer to my question because...

Dr Bossi: Right. Correct.

Dr De Bari: ...Again, if you want to have an answer, you should treat patients like in the Flame trial, in the experimental arm of the Flame Trial. In the POP RT trial...

Dr Bossi: Yeah.

Dr De Bari: ...Staged with the careful staging of the POP RT trial.

Dr Bossi: Correct.

Dr De Bari: ...And then you have an answer. So, I know that you could not, but moving in this sliding background, with patients that we see every day and that need an indication of radiotherapy. But there's no discussion about that, obviously, but how to deliver such kinds of treatments. When I arrived in Switzerland the hypofractionation was not still delivered, we introduced the hypofractionation following the CHHIP trial at the beginning, as you know, the CHHIP trial enrolls patients also with D3 tumours or Gleason 8. So, this kind of patient could be treated as the CHHIP trial as the Flame Trial, as the POP RT trial. So, sometimes it's difficult to take a decision to be medically sure because to be sure as a medical doctor is always difficult, but medically sure that we are doing our best for our patients. I agree with you and the data that you showed on the length of the duration of hormonal therapy with or without HDR are very interesting because for young people or for patients without major comorbidities, two or three years of hormonal therapies did not add a major toxicity. We are discussing about toxicity, not about quality of life, because it's another point, but in terms of toxicity could be acceptable in particular cardiovascular toxicity, in older patients or patients that have more comorbidities the fact of reducing the duration of hormonal therapy was already something that was showed by the ASCENDE-RT trial. The data that you showed confirmed that higher doses of radiotherapy delivered with HDR, in this case, could improve the outcomes of these patients that reduced the duration of hormonal therapy. And it's something that is interesting because we are discussing about a local treatment, the radiotherapy still remains a local treatment. But the three trials that you showed confirmed that we can have an impact also on systemic treatment, and it should be a message that our medical oncologists could probably be interested in.

Dr Bossi: Sure, sure.

Dr De Bari: There are no questions from the audience, so, if you do not have any comment, sorry, further comment, Alberto, I think that we can close this very interesting presentation. I personally thank you of your time and of your messages. And I would wish a very good evening to everybody. Thank you very much.

Dr Bossi: Thank you very much, Dino, thank you, it was a pleasure.