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Boost brachytherapy in prostate cancer

Dr Iturriaga: Hi. Good evening, everyone. It's a great pleasure to have the opportunity to share with you some moments in this evening and also, to talk about prostate brachytherapy. Before starting, I'd like to let you know that I'm going to do a presentation of this topic, Boost Brachytherapy in Prostate Cancer, and also, we'll have with us a very well-known specialist in neuro-oncology, a radiation oncologist working in Switzerland, Dr Dino De Bari. So, it's a great pleasure to have Dino with me. Thank you, Dino, for being there. And I'm looking forward to the discussion that we have after the presentation. So, before starting, it's important to let you know that if you have any questions, you can use the button of questions & answer that you can see in that slide. And you can ask whatever you want to ask. Dino De Bari and myself will be looking at the questions, so in case there is an important question, we will stop the presentation in that moment to try to answer them. If we believe that those questions can be answered afterwards, then, we'll wait for the end of the presentation to try to discuss all of them together. Okay, so, let's start with the presentation. First of all, it's important to know that when we talk about brachytherapy, there are two different kinds of brachy. One is the low-dose-rate brachytherapy, it's the older one, and also, the HDR brachytherapy. As you may know, LDR brachytherapy, in this kind of brachy, what we do is to deposit iodine seeds in the prostate, and with the HDR brachytherapy, what we do with the high-dose-rate brachytherapy is to insert into the prostate catheters or needles to send the radiation source through them, and stop into the prostate to deliver the radiation. Before continuing, it's important to note that I have an important disclosure. And the most important one is that I am a brachytherapist. I am a doctor specialised in prostate cancer, and I do everything. I do external beam. I do a lot of SBRT, but I also do brachytherapy. And I do really believe it's an important treatment to offer to our patients. And I'm going to try to show you which is the evidence today to say this kind of sentence. Okay. If you look at the source characteristics of the two different types of brachytherapy, the low-dose-rate brachytherapy, mainly, they have iodine seeds, they have a relatively lower energy, so, the source placement is critical. And also, it's important to note that no room shielding is required. However, with the HDR brachytherapy, there is a significant higher energy source and the dosimetry is more forgiving. And for this reason, I do believe that if you are thinking of starting a protocol with brachytherapy, HDR brachytherapy may be the way to go because it's easier to do and it's easier to give better treatment for our patients. Unfortunately, to do this treatment, we need a shielded room today. Okay. Prostate brachy, as you may know, is the superior form of conformal radiotherapy. It has a very tight dose-distribution, and it allows dose escalation beyond what is safe with external beam brachytherapy alone. And this has been demonstrated several times in different studies. Also, with the HDR brachytherapy, to get a great dose, a very nice dose optimization, we need the needle insertion, we also work with dwell position and also, with dwell times. And compared to LDR brachytherapy, we can say that HDR is high-density. With this, I mean, HDR implant has doubled the number of dwell positions versus LDR brachytherapy. And the seed usually have the same strength. But in the other hand, with HDR brachytherapy, the dwell times may vary in each position. So, we can play with the dose to try to make a better coverage and to increase the dose where we want. Actually, if you ask most of the brachytherapists or physicist experienced in brachy with both

modalities, most of them will agree that HDR brachytherapy gets consistently more robust dose coverage and a better normal tissue sparing. But before continuing, the most important thing here, and I do always say this sentence when I'm talking about brachytherapy, we have to avoid fights between radiation oncologists. We are in the same team. And what we want to do is to administer the most effective treatment for our patients. And what we finally want is to increase the chances of cure and maintain quality of life. So, this is the way to go. And we have to take this in mind when we talk about things. So, this is not a fight, we have to decide for our patient, the one we have in the clinic, which is the best treatment that we can offer. Okay, let's hear a little bit what happens with brachytherapy in monotherapy, because I'm going talk specifically about brachy boost, but before starting with that, I wanted to do a very brief summary of what has been published with LDR brachytherapy or HDR when we use this kind of brachy as a monotherapy. So, as you can see in this table, with LDR brachytherapy, we have very long follow-up, very large number of patients treated in different cities in the world. And as you can see, the cause-specific survival and the biochemical control rates are absolutely amazing. In low-risk, we are seeing biochemical control between 85 and 95%. And the cause-specific survival is approximately between 95 and 100%. So, if we use this kind of brachytherapy in low, or in favourable patients in low-risk or intermediate-risk, what we are going to see is very good results. HDR brachytherapy has demonstrated very similar results. As you can see here, this is a meta-analysis published last year of 14 studies. And you can see mainly the same thing. As you can see, the biochemical relapse-free survival of five years with low, intermediate, or high-risk disease ranges between 91 and 98%. So, very similar results with HDR monotherapy. Also, there have been studies looking at, what about erectile function. And most of the studies published have demonstrated that brachytherapy may be the best treatment option in case you want to preserve the sexual function. At least for sure, when we compare with radical prostatectomy, and for sure, if we compare it with at least other forms of external beam radiotherapy. The guidelines say that brachytherapy for low or intermediate-risk, but also for high-risk, should be offered for eligible patients. And this is very interesting, because I do believe that if you have in your department this kind of technology, we have to be aware of these guidelines and we should offer this treatment for our patients. In patients with favourable disease, in this case, favourable intermediate-risk disease, there is a very nice study, not published yet, but presented in ESTRO twice, in which it was a randomised trial comparing combination of external beam plus brachytherapy versus brachytherapy alone. This study showed that the results in terms of biochemical control was single between both treatments. However, the monotherapy arm had better low rates of toxicity. And this issue has been demonstrated in several studies. If you use combination approach or brachytherapy plus external beam then, you probably are going to get a little bit higher toxicity results. Also, there are a study looking at which is the treatment that allows a better quality of life. And this study was submitted to radiotherapy and oncology by one of the doctors working in Sunnybrook in Toronto. And they found that brachytherapy monotherapy is the treatment that gets the higher chances of preserving quality of life. Just a reminder, if there are any questions, you can use the question & answer button, okay? Okay. I want to go through several topics or concepts that I think are very important. One is the definition of cure. This is a very interesting study published two years ago by Dr Juanita Crook. A very famous radiation oncologist specialised in brachytherapy in Toronto and now working in British Columbia in Canada. And Dr Crook found that four years after LDR brachytherapy, you get a PSA level lower than 0.2 nanogram per millilitres. Then, the chances of cure are extremely hard. You can see there, between 97 to 99% at 10 years, which means that one of the most important aims when we do brachytherapy is to try to get a very low PSA nadir. So, this could be a good prognosis factor. Another important thing is always a failure after definitive local radiotherapy, is of important note or not? Because, as you can see, most of the data I've talked about during this presentation have been talking about biochemical relapse-free survival, or disease-free survival, but there's some data out there showing that maybe this kind of endpoints are not good surrogates of overall survival. But still, I do believe that biochemical control is a very important surrogate, and I'm going to try to demonstrate. We know if we look instead of patients with low-risk or intermediate-risk, if we look at high-risk disease, then we know that this high-risk population is at very high-risk of rapidly rising PSA at relapse. And they're more likely to die as a

result of prostate cancer, this high-risk population. Nowadays, also we know that if we'd use novel generation imaging in that relapse, we find, in most of cases, nodal or distant disease in this kind of population. And also, PSA relapse means more staging studies, salvage local treatments, and salvage systemic therapies. And from a patient perspective, this means anxiety, this means comorbidities associated with ADT, and also, it means that patient progresses to M1 disease, which can produce bone pain, fatigue, costs, and also toxicity of novel combination of chemotherapy or novel anti-androgen therapies. Some authors state that if you have a biochemical relapse, maybe you should not use ADT. This is right. But if you look at what it's doing, one of the most important centres in the world, in this retrospective study of almost 3000 patients published by Zumsteg in 2016, they found that patients with failure, especially local failure, they were receiving, almost 90% of them, ADT. So, this is the reality. Patients with average disease that relapse after treatment, they received ADT. If we get a treatment and we have treatment that can reduce this amount of biochemical disease or local disease, local failure, then, maybe we can reduce all these patients that received local failure. This is another very nice study published by Kishan in European Urology in 2020. This is individual meta-analysis of six randomised controlled trials. And we found that local failure is a very important prognostic factor, and actually, they found that local failure is a prognostic factor for distant metastasis. So, it's important to get the best local control in this patient that we can achieve with the best technique that we use. This is another very nice study published by a Spanish doctor, Dr Almudena Zapatero in 2020 as part of two sequential studies of biomarkers. Of course, the cancer, they looked at patients with positive biopsies after treatment, and they found that to have the positive biopsy was a predictor of metastatic disease afterwards. So, again, it's demonstrated in two sequential studies that local control is extremely important in this population. So, this is very well-known. I mean, there are a lot of studies shown in randomised controlled trials showing that if we increase the dose, we get a better biochemical control. This is very well-known. We can do that. But in the last years, there is a new friend in the game, a new technique, it's called SBRT, or, you know, you may have learned about it, and it's getting very nice results. The treatment is very easy to administer. Only five fractions in most of the series, and they are getting very good results in patients with favourable disease. Based on this kind of retrospective data, lot of doctors state that this is a standard of care and we can use it. And some of them state that patients with unfavourable intermediate-risk disease or high-risk disease, also may benefit of this treatment. But I think that we have to be a little bit cautious about it because the randomised controlled trials published to date are not looking specifically at biochemical control yet. There is only one study looking at it, and the rest of the studies only have published or documented toxicity. The only study published to date is the HYPO-RT-PC trial. It is a very nice study. And this study was almost 1200 patients, randomised patients of between 78 Gy of external beam versus SABR 42.7 Gy administered in 7 fractions. Most of the patients were intermediate disease. And after five-year follow-up, they found that there were no differences in terms of failure-free survival. This doesn't mean that SABR is better than external beam. The only thing it demonstrates is that the biochemical control is very similar between both modalities. It's important to consider in this situation that almost every single published study, retrospective, prospective, and randomised, comparing brachytherapy boost versus external beam alone, have demonstrated better tumour control outcomes with the combo strategy. So, if we have a patient and we really want to increase the chances of getting tumour control, combo seems to be the best options for these patients. There are two very important trials. One with HDR brachytherapy published by Peter Hoskin, and the other one published by Dr Morris in the journal in 2017. Both studies have demonstrated better biochemical control with the combo study. The first one is the ASCENDE-RT trial. This study used LDR brachytherapy combined with external beam versus external beam alone. They found, and this is very interesting if you look at the course, that during the five years, there was no differences between the course and afterwards, after the seven years and nine years, then the difference become more important. This also is important because we have to follow the patients for large periods of time. We want to show or detect differences in terms of biochemical control. The problem with this study is that in the patients that received low-dose-rate brachytherapy, the rates of toxicity, specifically the GU grade-3 toxicity was much more high, actually, the differences were 19% versus 5%, which is very high. And 50% of the toxicity were urethral

strictures. Some authors state that this is not what actually occurs in the clinic, in our patients, but it's actually what they published in the randomised trial so, we have to be aware of this. Probably, the most important problem for this is the migration of the seeds to the apex of the prostate. So, this increases the dose that is gotten by the membrane of urethra. And this is known to be the part, most importantly, in the development of urethral strictures. Now, this has been also very well demonstrated by this British group and published in the Green Journal a few years ago. The second randomised controlled trial is the HOSKIN trial. So, a trial in UK. They found, as I showed before, that with the combination of HDR brachytherapy plus external beam brachytherapy, the results in terms of biochemical control were better. And in this study with HDR, they didn't saw differences in terms of toxicity. In GU toxicity or in bowel toxicity. It seems to demonstrate probably HDR brachytherapy produces less grade-3 toxicity. I want to show you another published data. This is not published yet. This is a doctoral thesis and I'm the director. This is a match cohort analysis of HDR versus LDR boost in one centre with very high-volume of prostate brachy. And in two important groups of 200 patients each, they found that after a median follow-up of seven years, there were important differences in terms of toxicity. The toxicity was clearly higher in patients with LDR brachytherapy versus HDR brachytherapy. So, this is a retrospective study. That's the biggest study showing this, and this was presented in ESTRO last year by Dr Goni and would be probably published this year. Okay. There are also couple of very interesting points published recently. The first one is what happens in patients with very high-risk disease, with aggressive disease, between score 9 to 10. This study is published by Kishan in 2018 found that patients receiving combo strategies had better cancer-specific survival, better distant metastasis, compared to patients receiving other modalities such as radical prostatectomy alone or external beam brachytherapy alone. The second study is also a study published by Kishan last year. They found similar things. They found that patients receiving combo strategy, they had a very low distant metastasis free survival compared to the patients receiving external beam or radical prostatectomy. But there has been another very interesting study that looked at very similar outcomes. This is a study published in JAMA oncology very recently by Dr Derya Tilki that is a very well-known urologist working in Martini-Klinik. And what they found in this study is, they were not just looking at radical prostatectomy or external beam. They divided the groups in maximum radical prostatectomy versus maximum radiotherapy. They defined maximum radical prostatectomy as radical prostatectomy plus adjuvant or salvage radiotherapy plus-minus ADT, and maximum radiotherapy was considered brachytherapy plus external beam plus ADT. And they found that when maximal strategies are used, multimodal strategies are used, then, the probability of biochemical control and prostate cancer-specific mortality are reduced when this multimodal treatment are used. It's very interesting stuff. Okay. Few more concepts. Very recently, it has been published this FLAME trial. In this study, this is a randomised trial comparing patients receiving dose of 77 Gy in 35 fractions versus patients receiving 77 Gy to the whole prostate plus a focal boost to the dominant lesion to 95 Gy. This has been published in JCO, 2021 and they found with a median follow-up of six years that there was a biochemical control advantage in patients with increased dose. This is something that has been very interesting in the radiation oncology community, but we already knew it. We know that increasing the dose to the prostate, to the tumour with brachytherapy, we get this kind of very interesting results of better biochemical control. There are a few comments on this study. First, this is the first study demonstrating dose escalation, focal dose escalation with external beam alone improves outcomes. Second, most of the patients in this study were high-risk disease. This mean that probably most of the study had multifocal disease, and to do focal boost to multifocal disease is quite difficult with external beam. And third, 35 fractions, maybe, is not the way to go in this data in which we are using extreme hypofractions. However, brachy boost, we know that the evidence showing that their increase in biochemical control rates is very high. It allows to increase the dose to the whole prostate, not only to a part of it, and also it reduces the length of the treatment. So, this is all important to take into account. Also, HDR brachytherapy is interesting for things like salvage treatments and it seems like it's very low in terms of toxicity compared with LDR brachytherapy. There are relative contraindications and difficulties in the operating room to do HDR brachytherapy or LDR brachytherapy. These are patients with very large prostate, or very small prostates are more difficult to implant. Also, the urinary symptoms. More importantly, if there

are obstructive symptoms, it's important to consider because brachytherapy may produce higher urinary toxicity and also, patients with prior transurethral resection of the prostate and with a big urethral defect. These patients are more difficult to treat with brachytherapy. Also, it's well-known that if you use neoadjuvant ADT, then, a higher toxicity can be expected for these patients. Also, another important point to consider if we are going to offer brachytherapy, is the T-stage. We know that HDR brachytherapy catheters are safely implanted outside of the prostate, so, in case of T3 disease, it's easier to do HDR brachytherapy instead of seeds because of the risk of migration of the seeds in the prostate. As I was saying before, TURP defects are also important. And this is also an important point. The anatomic issues, volume changes over time. LDR brachytherapy during the lifetime of dose delivery may occur anatomic changes. First, oedema after the implant and the first weeks of radiation dose, because the LDR administers most of the dose in the first two months. And also, the shrinkage of the prostate in patients when ADT is used. Also, in HDR brachytherapy, the full dose is delivered within minutes to hours of planning, the confidence is better with real time HDR brachytherapy. Other things that you can use to increase the way we do brachytherapy is dose painting. It's very easy to adjust the doses and increase the dose where we want. For needle, example, it's easy to implant needles in the seminal vesicles and treat the seminal vesicles to a very high-dose of radiation. And also, we can use TRUS-MRI fusion to get nice distribution of the dose in dominant intraprostatic lesion. I do believe that further innovation will go by using dose painting to dominant lesions, and to administering broader margin with the help of MRI. And MRI is a crucial element to plan HDR brachytherapy. And to finish, there is a very nice trial led by Andrew Loblaw. This, to my knowledge, has not yet started, but it will start probably this year. And I want to show you just the trial's schema. This is gonna be patients with unfavourable and intermediate-risk or high-risk disease. These patients are going to be randomised to 46 Gy in 23 fraction or 25 Gy in 5 fractions, or both these plus ADT plus a boost with LDR or HDR. The other arm is very interesting because it's gonna be a combination of all pelvis plus the boost with SABR. So, the pelvis is going to be treated with 25 Gy and the prostate will be treated to 40 Gy in 5 fractions, everything. This is gonna be very interesting because SBRT, finally, in this study. So, that gets us good results as the brachy boost. Then, brachytherapy is probably going to be less used in the future. And SABR probably will be used more commonly because it's not an invasive procedure. So, in my opinion, the future is collaboration. It's time to define and to individualise which is the best radiation technique, brachy, SABR, external beam. Which is the best treatment strategy? We have to continue treating the whole prostate or if it's important to increase the dose with a focal boost. Also, it's important to note or to define if we need to combine different techniques. And I do believe that the use of novel generation imaging such as MRI and PSMA PET for staging and volume definition will improve the data that we have nowadays, and also, in the future. Also, we will have to test whether the novel anti-androgens may have a role in these patients of high-risk disease. But for the moment, if you have a patient in the clinic and you really want extremely low PSA values after the treatment, higher biochemical and local control, and a treatment that allows not only for a focal, but for a whole dose escalation into the whole prostate, then, in my opinion, and that was my disclose before starting, is that the best treatment strategy is the combination of brachytherapy plus external beam radiotherapy. And this is it. Thank you so much for your attention. And I'm looking forward to the discussion with Dr De Bari.

Dr De Bari: Thank you very much, Alfonso. A very comprehensive and nice value of the data that are available now on this issue. For instance, there are no question I would like, only to be a bit provocative, and you know that I like it. So, it's not against you. It's just for the discussion. As you said, that you are a brachytherapist but at the same time, you also deliver SBRT in quite usual situations. So, you can say no conflict of interest in this sense. So, it's nice to discuss with you about that. I'm a bit struggled when I look at the guidelines that you showed. You showed only one of the guidelines that is available. But as you know, also in CCN, they say the same thing that you said. The Canadian guidelines say exactly the same thing that you said. So, everybody said, you must make brachytherapy because we have at least three randomised trial that support the adoption of brachytherapy at least as boost, we do not discuss about monotherapy because it's not the goal of the presentation, but everybody said you must use brachytherapy. But when we look at all over the world,

the centres that knows how to deliver brachytherapy is becoming more or less smaller. So, everybody wants to deliver brachytherapy, but I think that the number of centres that can do that is becoming smaller and smaller. And it's clearly something that we should face in the next year. Also, looking at the data of SBRT that has been usually adopted as monotherapy, but it's exactly the same history that we had with brachytherapy. We started with monotherapy, and then we added it as boost. And when we look at the availability of such modern technologies, MRI-LINAC rather than CyberKnife, you can deliver quite good, not as good as brachytherapy, I completely agree with you. It's not the same thing. But in any case, you can deliver good treatments with SBRT. How we can still support SBRT in 2022, looking at the data that are available? I say to you. It's a provocative question, but it's just to say that the real life is quite different from the guidelines and I'd like to try to understand how to manage it.

Dr Iturriaga: No, I mean, I know you used a provocative question, but it's interesting because it's the reality. It's what we are facing during the last years. Actually, you know that I'm very involved in the GEC-ESTRO brachy group of the European society in the prostate brachy group, and there is concerns about it because there is quite clear in the evidence published today that the combination of HDR or LDR brachytherapy plus external beam allows to get better control of the disease. Unfortunately, worldwide, the adoption of this kind of treatments is going down instead of going up. So, there are several issues explaining this thing. One of them is the training issue. This is a treatment that is delivered and done in the operating room, and we are radiation oncologists, so most of us, we are not used to work in the operating room. And this is something important because young doctors are not used to this, and the training is losing the training strategies in several countries. The second thing is that technology is, most of the time, so it very frequently happens that with the technology, we are kind of very impressed about how nicely we can do things and how nicely we can deliver the dose if we are going to the operating room, we don't have to use any needles or catheters or whatever, and there is not going to be blood anyway, anywhere. And we are able to deliver very nice dose of radiation. And I do believe that in the future, this kind of novel strategies such as probably SBRT, demonstrates that the control of the disease is as good as the combo with external beam on brachy. Brachy is going to be less and less used. I think that we have to be a little bit cautious because the only trial to date published looking at biochemical control between external beam and a kind of SBRT, because it's not actually an SBRT, the dose administered in the HYPO-RT-PC trial, they found exactly the same results in terms of biochemical control. So, when I talk about this, I usually say be cautious because in my own opinion, conventional external beam radiotherapy does not get enough good results in terms of local control in patients with high-risk disease. I do really believe that we have to improve outcomes in that situation. And as I was saying before, the option to improve these outcomes is to better increase the dose in the prostate. This for sure, LDR or HDR brachy, is the way to go. But also, if you can do it with external beam radiotherapy, such as SBRT, of course, will be the way to go. And we have also another friend in the field now. That is the combination with novel anti-androgens. There are several studies on going right now, looking at the combination of high doses of radiation plus novel anti-androgens and we'll have the results probably in a couple of years from now, but this is also going to be probably a game changer in this situation. So yeah, you are right. I mean, there are some doctors as myself that we love brachytherapy, we do brachytherapy. We really believe that is the best way to go. But if other techniques that do not need to get into an operating room, you don't need to anaesthetise the patient, then, probably are going to be the techniques used in the future. And for that answer, the most important study is the trial that I showed you. The Loblaw trial. Because this trial, I do believe, is going to give answers about it. The problem's gonna be that if the trial shows that brachytherapy is better than SBRT, probably we have to start training a lot of people all over the world, again.

Dr De Bari: Okay. Thank you. I was quite surprised looking at your advice. Seeing that, but it's another question. In the Canadian trial, they decided 5X5 Gy is like of a standard arm, standard treatment for the pelvic. It's strange that we have only four phase-II trial of standard, it could be, you can say, not a bias, but in any case, we are evaluating SBRT against brachytherapy. And we also add something that is not exactly a standard of care in the trial. It seems to be quite surprising. And also, there are no questions from the

audience. I think that we can enjoy our summer evening. And I would like to thank you very much for your nice presentation, for your availability. And I hope to meet you soon and please, enjoy your summer. Thank you very much.

Dr Iturriaga: Thank you. It has been a great pleasure.

Dr De Bari: Bye.

Dr Iturriaga: Bye.