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Ultrahypofractionation in breast cancer

Prof Poortmans: So, thank you very much for participating to this session about Ultra-hypofractionation in breast cancer. My conflict of interest is not related to this session, not at all, it's about Intraoperative Radiation Therapy, and especially, the research into FLASH radiation therapy. Now, this slide you will see several times, don't forget to put your questions. We will have a short break in between to have the most pertinent questions discussed, and then, at the end, we have enough time to discuss it more into detail. So, this is the overview of my presentation, and I will start with an introduction and the basic of radiobiology because this is important to understand what hypofractionation, and especially Ultra-hypofractionation is about. Since the 24th of February, I include always one slide on this, what is unfortunately ongoing in the North East of Europe. So, what changed? I started training many years ago, and we learned field-based radiation therapy. It was two-dimensional, making a transition to three-dimensional, and the first attempts to static IMRT were there, but today, we have to speak about volume-based radiation therapy, where IMRT and VMAT become more and more the standard. And we are continuing this evolution, of course, not to the same speed in all tumour types, to radiation therapy, which is adaptive, either to changes in volumes or in movements or even functional, so based on the biology. So, the techniques in radiation therapy are very important, but they serve a goal. It's not about the technique in itself, the most important is that we hit the target. So, for this, we need to treat the right target volume. ESTRO, which started after the first ESTRO course in breast cancer wrote, developed these guidelines on target volume identification and contouring in breast cancer, which is now used in many places worldwide. And it is about volumes, forget about fields. I know that, unfortunately still today, a lot of our colleagues are thinking in fields, thinking two-dimensionally, and then, constitute some target volumes to go to even volumetric IMRT, but that's not the right way. And we know that there is quite some variation in target volume contouring, two examples from the Netherlands for the breast alone, but there are many others. So, ESTRO helps in learning this contouring with contouring exercises. This is an old example from an old ESTRO course, where you can see that there was a huge variation in contouring of the breast compared to, at the right, the expert contour, and this has a huge impact. Look at what you would have, is a CTV, so you need to add a margin to PTV and then do the penumbra. If you just would put two tangential fields in the expert contour-based setup, you would treat hardly any part of the heart. In the most extensive target volume, you would include one-third of the heart to a very high-dose. So, these modern techniques led us to do a better more homogeneous treatment planning, but you have to start from CTVs from clinical target volumes. And yes, this has a benefit. This is so-called simple IMRT. This is not real IMRT, it’s just using basic compensators or a very simple skilled in field. It dates from 15 years ago and already then more homogeneous dose was shown to be beneficial for the cosmetic outcome. A technique that we developed when I was still working in Tilbury in the Netherlands for the internal mammary lymph node irradiation in the framework of the EORTC trial, it was a single isocentre, four main fields, three gantry angles. This is from, as you can see 2006, but the techniques dates from 1995 when we even didn't have a CT scan, we had a simulator with the CT extension. So, we could make up to five slices, not more than that,

but you can see that even in 2006, we got quite favourable dose distribution, including the internal mammary lymph nodes with the dose, which is even for nowadays standards, acceptable to lungs and heart. And the next step is, of course, to combine 3D radiation therapy or volumetric IMRT with breath hold. And you can see that by combining those techniques, you considerably lower the dose to the heart and to the lungs at a slight increase of the dose to the other breast. And there are even much more opportunities because this publication dates from 2014. So, these techniques are already 10-years-old. So, don't forget to have your questions. Radiobiology. What we look for is a broad therapeutic window, a therapeutic window, which is the space where you can have tumour control without late normal tissue effects. The broader the therapeutic window, the more favourable radiation therapy can be. So, what would this be in hypofractionation? A lot has been debated about it. When we speak about hypofractionation, we should not forget, it's not only about dose per fraction, the number of fractions, but you always have to lower the total dose. If not, you increase the total dose and you increase the side effects as has been shown in some early experiments in the '70s. For the non-radiation oncologist, a simple comparison. If you take a big hammer and you hit very strong, or you do it very gently, 10 times with a small hammer, in Newton, in power, it's exactly the same, but you'd know from radiation therapy and also if you would do the same exercise with the hammer, that the effect is absolutely not comparable. So, the linear quadratic model is where we base our calculations on, and this is not new. The linear quadratic formula is from 1976. So soon to become 50 years young because it's still usable. What does it do? It shows how tissues react to changes in fractionation. So, it's sensitivity to fractionation. And for breast cancer already quite early, we found out that the alpha/beta, in contrast to other tumours, is quite low. It's also low, for example, for prostate cancer. In general, for early reacting tissues, acute reactions, and for most cancers, alpha/beta is high, for late reacting tumours and tissues, and for breast and prostate cancer it's low. So, based on this, it becomes attractive to use hypofractionation instead of conventional fractionation. And this formula has been used for the calculation of the equivalent dose in the first trials. This is the example of the English trials. The START A trial where the 50 Gy in 25 fractions was compared to 14, 15 and 39 in 13. And based on alpha/betas, an equivalent dose was used. Note that the dose per fraction goes up and simultaneously the total dose goes down. Don't forget your questions. So, let's go into the first part of the evidence and then, have some questions from you, if any questions arise. The proof of the pudding is in the eating. So, let's start with the moderate hypofractionation. We have the Canadian schedule, they were the first to publish a large study on hypofractionation, and they later published it with a much longer follow-up, showing that 42.5 Gy in 16 fractions is quite equivalent to 50 Gy in 25 fractions. So, the dose perfection goes up, the total dose goes down, local control identical, side effects identical, and also identical after 10 years of follow-up. In fact, nothing changed after 5 years compared to 10 years, the slopes run perfectly parallel. Of course, there were influencing factors. For example, the times in treatments, the age and the tumour size, by the way, age isn't protective, young age is protective. It's often forgotten, but older patients are more sensitive to late side effects. Fractionation was absolutely not an important factor for cosmetic outcome. The English published also a series of studies. The START trials, the most attractive is START B comparing the 40 Gy in 15 fractions with the 50 Gy in 25. And if there would be a difference, it shows that 40 Gy in 15 fractions might even be a little bit better than 50 Gy in 25. Anyway, and also the other trials confirm that if there would be something, it's in favour of moderate-hypofractionation. Morbidity here, it's clear, it favours 40 Gy in 15. So, the 40 Gy in 15 seems to be a little more gentle for the normal tissues. For the chest wall, we have the Beijing trial that compared 820 patients, 15 fractions, total dose of 43.5, a little bit exotic compared to the 50 Gy in 25. Unfortunately, this study had a lot of limitations, including the very old-fashioned radiation therapy protocol, but they limit it to really high-risk patients. And you can see absolutely no difference, neither for local control recurrence or for acute and late toxicity. However, note that the five-year local recurrence after mastectomy was nearly 10%, which is not a conventional figure. Nowadays, in databases, in other studies, we are around five years after mastectomy with post-mastectomy radiation therapy in general, below 1 to 2% recurrence rate. So, this was high-risk and not optimal radiation therapy techniques, but the key-message is no difference between moderate-hypofractionation or conventional. So, the pudding is good and can be eaten. Now, where is the limit? The

first study, and this is very important to realise the FAST study was not done to prove that Ultra-hypofractionation is as good as conventional fractionation. So, three groups of around 300 patients were treated to either 25 fractions of 2 Gy in five weeks to a total dose of 50 Gy or 5 fractions once a week, also in five weeks of 6 Gy to 30, 5 fractions of 5.7 to 28.5, calculated on assumed alpha/beta values and published with a follow-up of 10 years. The endpoint, and this is hugely important to realize, it was photographic breast appearance. It was not powered to detect anything about local control. That was only a secondary endpoint. However, with three groups of 300 patients and 10 years of follow-up, something could be said, especially on the late side effects, most late side effects early, where with conventional fractionation, the moderate change in appearance at 28 months and the marked change in appearance was worse with 5X6 Gy. So, 5X6 Gy is inferior for breast appearance, cosmetic outcome compared to the other schedules. The 5X5.7 in five weeks was identical to 25 fractions of 2 Gy. So, for breast shrinkage, again, no difference here, a clear difference in this favour of 5 fractions of 6 Gy, based on this alpha/beta calculation for breast shrinkage of 2.7 was estimated. And then, the study, the FAST-Forward trial, which was published just in the early days of the COVID pandemic, comparing the new conventional, new standard of 40 Gy in 15 fractions with 27 or 26 Gy in 5 fractions in five consecutive days, in one week. So, patients were randomised to those three randomization arms, eligible patients had a locoregionally early or moderately advanced, no real advanced disease. So, follow-up was done up to 10-years with cosmetic evaluation and PROMs. Here the primary endpoint was ipsilateral breast tumour recurrence. So, here, it was powered to detect a difference to see whether there was equivalence and with 4096 patients, and a follow-up of six years, 5.96 years, you can see that acute skin toxicity was lower with the 5 fraction regimens, especially shorter lift. If you compare it with the three-week schedule, it lasted for several weeks longer, both for grade 1 and for grade 2, and thanks to the modern radiation therapy techniques, grade 3 acute skin toxicity is virtually not existing anymore. Ipsilateral breast tumour recurrence, it's seen in all those studies, no difference. And the upper study is 40 in 15 then comes at 27, then comes at 26. But of course, from a statistical point of view, there is no difference ipsilateral breast tumour recurrence. There is a non-inferiority strongly confirmed. Disease-free survival, absolutely no difference, but then, become to the late adverse side effects, here the 27 Gy in 5 fractions is inferior. We see more clinician assessed late side effects, and you can see it here, at five years, the adverse effects in the patients who received 27 Gy was very much only a couple of percentage, but 15% had quite a bit at first side effects while the 40 Gy in 15 fractions and the 26 in 5 Gy, there was no statistical and no clinically relevant difference. The conclusion is that for local control, the two Ultra-hypofractionated schedules are non-inferior compared to moderate-hypofractionation, but for late side effects, 26 Gy in 5 fractions is quite similar to 40 Gy in 15. And now, it might be shocking for some, but the 27 Gy in 5 fractions is more consistent with 50 Gy in 25 fractions. If you compare 40 with 50 and 50 in 25, then you see that 40 Gy was more gentle. And the 27 is a little bit more impacting at the level of 50 in 25. So, there are a lot of benefits and it was rapidly adopted, not as a COVID measure, something temporarily, but it was adopted to stay as the new standard in the UK and more and more other countries. And let's now have a short interruption for questions, Ivica and Pierfrancesco, did you see questions or do you have questions yourself?

Dr Ratosa: Thank you, Professor Poortmans, for the first part of the presentation. There are no questions from the audience, but maybe just a short question regarding treatment planning. When we apply higher doses per fraction with 5 fractions. So, per FAST-Forward protocol, they were applying simple 3D techniques. And usually with maybe more advanced techniques we can reduce, improve homogeneity in the target. So, is the technique important or as long as we gather requirements in the target and dose to organs at risk, the technique doesn't matter?

Prof Poortmans: Ivica, thanks for the question though. It's very important to have a proper technique. It was indeed a study, which is around a couple of years ago. There is a appendix, which you can download from their website on how treatment planning should be done. And it's a basic 3D dose homogenization model, not yet an advanced fluency optimised dose homogeneity, for example, but it's breast alone. And for breast alone, I agree with many who state that for breast alone, we don't need very fancy techniques for most of

the patients, for at least 80% of the patients. The basic setup with two tangential fields adapted in shape to the anatomy-based target volume and with an optimised dose homogeneity using fluency, for example, for most of the patients, that will do perfect. And for some patients with very large breasts or a particular anatomy, we might need other techniques. And all this is valid for every radiation fractionation schedule. I will show in the remainder of my presentation that yes, dose homogeneity is very important, but it is not depending on the fractionation schedule that you use.

Dr Ratosa: Okay, thank you. We have also... Should we finish? I mean, we can have another question? Maybe, we can answer it right now. So, what those constraints should we use for the heart and lungs when prescribing moderate and Ultra-hypofractionated radiotherapy for breast cancer?

Prof Poortmans: Excellent question. Now for the Ultra, sorry, for the moderate-hypofraction, it's very easy, it's the same as for 50 in 25, we should not adapt our dose constraints. For the Ultra-hypofractionation of course, we have to adapt. The V20 for the lungs for example, in 5 fractions is something completely different compared to in 25 fractions. But for that we downloaded the FAST-Forward package and we used their prescriptions. So, I don't know them by heart, but we adapted those. And I will show why it doesn't matter between conventional fractionation and moderate-hypofractionation. I will show in a graph. Okay, I continue.

Dr Ratosa: Yes, please.

Prof Poortmans: Good, so, let's discuss. Now, first critique is the follow-up is too short. For Ultra-hypofractionation, we need longer follow-up. We need 10 years. And for example, NCCN world famous, they did not recommend, they do not recommend the Ultra-hypofractionation from the FAST-Forward. However, for patients who have difficulties in travelling and old, and frail, they can be treated with FAST. This does not make any scientific sense. FAST-Forward was prepared and was calculated statistically to detect non-inferiority in recurrence. The FAST trial was only a study for cosmetic outcome and to show a proof of principle. So, a trial which was not powered for ipsilateral breast tumour recurrence is accepted as a possible standard, while a trial, which was powered, which met its endpoint is not yet accepted and longer follow-up is asked. So, this is a serious issue, so, let's look into what we have. First of all, you all know the famous boost, no-boost trial, look at the local recurrence risks. What is changing after five years? Relatively speaking, nothing. The relative and absolute figures, a little bit. The benefit at five years with the boost was 3%. And at 20 years it was 4.4. The relative difference decreased even. So, once you have your five years, the slopes are quite parallel. There are no clear evolutions in the rates of recurrences comparing one schedule to another. This is just a boost, no-boost trial. So, it even decreases over time. This is the... That's an error for me, that is the moderate or severe fibrosis. So, what you can see is that the moderate to severe fibrosis at five years, the absolute difference was 11%, which is an increase with 104%. And look at 10, 15, 20 years, it's 15%, it's doubling. So, also here after five years, the slopes run perfectly parallel. There is no relative disproportionate increase in moderate or late fibrosis. So, they remain stable. Look then to the Canadian schedule, the Canadian schedule once five-year passed, nothing changed till 10 years for local control. And for side effects, 5 years or 10 years, nothing changed. Look at the START B study, no changes after five years. The two slopes run perfectly parallel for local control and for side effects. Five years, ten years, the slopes run perfectly parallel. That means that the follow-up is long enough at five years, same story. And I have other examples that I will spare for the sake of time. So, for side effects, there is no relative increase after five years, the slopes run parallel. For local control, exactly the same. So, there is no reason to fear that the results at six years will be completely different at ten years or at 15 years of follow-up. Then, this was the question from Ivica, dose inhomogeneity is a big issue. Well, we know that a patient with a big breast, if you have inhomogeneous dose, 112%, you might have an issue that you have more importance with hypofractionation because the 112% for 2 Gy is 2.24, 112% for 3 Gy would be 3.36. So, the relative increase is more dose. So, this is called the so-called double trouble described by Withers already in 1992. So, we have to adapt our fractionation with the prescription. So, the total dose needs to be adapted. So, a higher dose, theoretically, a higher dose in hypofractionated radiation therapy might be a triple trouble issue because your alpha/beta

uses the absolute dose. 2 Gy with 10% overdose is 2.2, but with alpha/beta correction, it's even more important. So, if you give a hypofractionation a higher dose, it counts even double. So, this is triple trouble. Now, is this true? Well, make some calculations. If you use an alpha/beta of 3 and you have a 105% dose homogeneity, which is in general what we accept nowadays on a volume up to 2 cubic centimetres. For 2 Gy, 105% would mean 53.6. For 2.7 Gy, 53.7, for 5.2 Gy, 54.2. This is nearly no difference. This to double trouble and triple trouble is in fact a theoretical issue. If you make the right calculations, it's not an issue anymore. So, this is not at all a concern, even not in patients with larger breasts. So, I don't say that those homogeneity is not important. No, on the contrary, my statement is clear for what I just said to Ivica, yes, a dose must be very homogeneous, but this has nothing to do with the fractionation. And again, this comes because we lower the total dose. Then, it's only validated for limited patient population. Yes, this is true. If you look into, and we published this very, very recently in the breast, all trials together, if you look in those which patients have been included, we have a lot of data on moderate-hypofractionation for whatever patient group. So, moderate hypofractionation, we can use for all patients. Theoretically, we could say we don't have enough data for patients after immediate breast reconstruction, but as we know that 40 Gy in 15, is more gentle for the normal tissues. I would rather say it's an extra reason to do moderate hypofractionation. However, for patients who have Ultra-hypofractionation, we have only data on breast-only and chest wall-only, but let's make some calculations outside of the target volume. The same patient I showed before, 2006. So, this is not something which is very fancy and cannot be done by everybody. This is 16-years-old, and this was the dose distribution, and look in detail. The brown is the lung and the green is the heart, 2006 left-sided, including internal mammary lymph nodes without respiratory control. So, please we can do at least as good in 95% of our patients. So, that means that the heart and the lungs do not receive 2 Gy or 2.66 with moderate hypofractionation. No, they receive something let's say between 25 and 75% of the prescribed dose. And if you'll then calculate the dose they receive, it's let's say between half Gy and 1.5 Gy for conventional fractionation, between 0.67 and 2 Gy for moderate type of fractionation. And then, calculating this for the Canadian or for the START schedule, you can see that with a realistic scenario, alpha/beta for late normal tissues of 2 and 3.5 for breast cancer. You can see that in the range that gives some dose to the heart, 70%, 50%, which we really try to limit, but because of the lower dose per fraction, you can see that the final dose with hypofractionation, even with the warm Canadian schedule is lower compared to conventional fractionation. An optimistic scenario alpha/beta... and this is probably very true, alpha/beta 3 for late normal tissues and for breast cancer, you can see that we considerably lower the effective, the biologically effective dose to heart and lungs in the range where they are treated though by hypofractionating, and the worst-case scenario, alpha/beta 1 for heart and lungs and 5 for breast cancer, even then, we are completely at the same level. So because we do not include a significant part of our lungs and we do not include our heart to the very high doses, we spare thanks to hypofractionation. So, I made those calculations on purpose for this presentation, a little bit more extensive. So, we go back to the 20th century with an alpha/beta of 2 and an alpha/beta of 10, and we compare it to the START and the Canadian studies, you can see that the START and the Canadian schedules for an alpha/beta 2 as well as for an alpha/beta 10 are lower compared to 25 in 2. And don't try to figure out how it comes, it's very easy because the total dose is so much lower. So, by lowering the total dose, you lower the overall impact and look into... I'm afraid there is some more animation here, look into what we do with FAST-Forward. So, if you look into the new schedule, FAST-Forward, alpha/beta of 2, your radio-biologically effective dose is 50 to 70% range, it's lower even compared to the START B study. And if you look with an alpha/beta of 10 for acute reacting tissues, what you expect it's much lower. And this explains why we see so much less acute skin effects with the FAST-Forward trial. Not only because it's only one week of irradiation, but also because the RBE is much lower. This in a graph, the LQ model compared to trial results. Now, it's just a fact that 40 Gy in 15 fractions is slightly more gentle for late normal tissues, especially for the acute reacting. And if you look in the FAST-Forward, it's even more gentle. Once you pass your alpha/beta of around 1.5, you have theoretically calculated, less side effects and this fits to the clinical outcomes in the trial where we see considerably less acute side effects. So, the mathematics match the results and the explanation again, is that a total dose is significantly reduced to compensate for

the increasing RBE on the tumour by increasing the fraction size. Then, the major critique, our hospital direction doesn't like it because we have, originally, we have three R's. Then we had a fourth and then a fifth and the most important is the sixth, which is reimbursement. There are a couple of papers published on this. This is one that we did worldwide. We made an inventory of the impact of moderate type of fractionation compared to conventional, well in 30 to 40% of the countries, the decrease in reimbursement is 60%. So, really, and some more calculations can be read in the manifesto from EBCC, where it's penalised severely in many, even in most countries. So, I calculated it extensively on a French centre data from 2019. So, switching from conventional fractionation to moderate-hypofractionation would lower the reimbursement by 39%. Also, not giving a boost in breast-conserving therapy to all patients, but to a more reasonable percentage of the patients. And if you'll go to Ultra-hypofractionation, there is even a further loss compared to moderate-hypofractionation of 23% and compared to conventional hypofractionation of 53%. So, directors absolutely don't like it. It varies from country to country, but in too many countries, it has a huge impact. And then, it's not only for radiation oncology, it's also for medical oncology, for surgery, for whatever, there are a lot of examples were better for the patients than the healthcare system treatment cannot be applied because of reimbursement. So, this is the most serious issue. So, before concluding, I suggest that we have the further questions.

Prof Franco: So ... I don't see any question coming from the audience. So, Philip, I have always like a clinical struggle that I face in the clinic when I treat patients. So, I normally use Ultra-hypofractionation quite in a relaxed way, I don't have any scepticism, or any fear like to treat patients. I treated, let's say, a hundred patients so far with Ultra-hypo, so, I'm okay with the clinical result and the way the logistic also is very, very important. One point that I always I'm a bit struggling with is whenever the patient needs to receive a boost. So, we know that the indication for the boost now, it's more selective than the past. We tend to treat a patient with a boost only in selected cases, in high-risk patients. And whenever using the Ultra-hypofractionation, we have some, let's say, uncertainties, if we want to do an integration of the boost in a concomitant boost or simultaneous integrated boost on how to integrate, maybe we also have it with mild-hypofractionation, but it's even more striking in Ultra-hypofractionation. And then, of course, we can treat of course, sequentially, but then, if we use conventional fractionation to deliver a boost, then, we would add an extra week, which is a little bit striking because we're using Ultra-hypo and then, if we hypofractionated the boost, then, we would still add some more fractions. So, what's your suggestion? And then, how we can best frame the fractionation in this case?

Prof Poortmans: I think you gave the most important part of the answer that is give it only to selected patients. Unfortunately, in many countries, including Belgium, where I live now, it's not doable because of reimbursement issue. So, the problem is that reimbursement has a major impact, not on fractionation, but on delivery of boost. So, in Belgium, most patients get a boost like in France and in many other countries. If you look in the Netherlands, there are publications about it, where the boost use is decreasing over time. The UK and Denmark are around 15% of their breast conserving therapy. I think that might be a little bit low, but I think it will be between 15 and maybe 30% at the highest that really have a benefit of a boost. So, we stopped boosting patients who have primary systemic therapy and have a PCR. Even a patient of 29 with triple negative cancer, if you have a PCR, why boosting? Please, if you have a lumpectomy and a tumour-free margins are 1.5 centimetre, congratulations to research and the boost foully mistaken out, no boost. So that are the ones that we are now using. And those that we boost and have a low risk, try to get those volumes as small as possible, really boost as small as possible, the core of the original tumour side, but not more than that. And then the fractionation. So, there are several groups currently are working on a SIB, Simultaneous Integrated Boost. Anna Kirby is busy with it, but I'm also involved in others. So, it's one of the discussion points at the upcoming Skagen Brainstorming Meeting organised in the north of Denmark by. So that's for sure one of the upcoming topics. Then there is for example, the Genesis Care Group in Spain, who treated now around 1,500 patients with FAST-Forward with simultaneous integrated boosts. So, they're collecting their data, they're following up their patients. So, that's also excellent work to present real-life data. What

we do or did at Antwerp during the COVID. We tried to limit the number of visits as much as possible. So, we gave a single boost of 6 Gy to as small as possible volume. Now that COVID “pandemisery” is over, we cannot use it anymore because there's absolutely no evidence. So, we started an in-house trial, prospective randomised. We need 120 patients to check at three years of follow-up the cosmetic outcomes. The accrual is running perfectly. And our standard currently is 5X2 Gy compared to 1X6 Gy. And we will see what the outcomes are, but I think that either a simultaneous integrated boost or a single moderately-sized, no small-sized, but moderately dosed boost would be another option.

Prof Franco: Yeah, that's great. It is also like reasonable from a logistic point of view. I think, Philip, there's another question coming from the audience. And this goes back to the topic of reimbursement that we touched upon briefly beforehand. So, is there anything we can do as clinicians to determine the change of reimbursement from the payment fraction to another type of reimbursement that doesn't penalise the institution, if implementing hypofractionated schedule?

Prof Poortmans: Yeah, we, as single doctors, we cannot do a lot, so, what you can do as a single doctor when you give a lecture to whoever presents his data, show this, make it as a point of attention. That's also why at the EBCC last year, it was the manifesto, it was about equal access to quality cancer care, were reimbursement in screening, in reconstruction, in one-day surgery compared to hospitalisation. The trastuzumab subcutaneous versus intravenous, that had all a major impact on reimbursement. So, it's not only about radiation oncology, that's why this should be a multidisciplinary activity. And we have to involve our patients in this. The manifesto is co-authored by patients. And they have to do also the work, and they have to knock on the door of the politicians. The manifesto has been sent to all countries to the European Commission, and at the very end they have to do it. And unfortunately, when money is involved, it's different to get minds changed.

Prof Franco: Great.

Prof Poortmans: Is it time, maybe, I make my conclusions?

Prof Franco: Thank you, Philip.

Prof Poortmans: So, conclusions. Trust in hypofractionation and aim at homogenous dose distribution, like Ivica already mentioned before, but this is independent of the fractionation schedule. For me, all patients in Antwerp have the FAST-Forward 26 in 5 fractions in one week, for breast only, chest wall only and partial breast as well. And we include even the patients who have a low risk for nodal involvement, let's say the Z11 patients, but they were treated with the old-fashioned tangential fields. So, most of those patients received a significant dose to the lower part of the axilla. So, in that case, we do target volume contouring of level 1 and the lowest part of level 2 and rotor, and we stay underneath the brachial plexus, the vessels, and of course, the plexus. And then, we also do the 26 in 5 but not for rear nodal irradiation. For frail patients, this was just to show that we published already our first experience, and this was very, very early introduced. Then, the FAST fractionation, the 5X6 or 5X5.7 can be used for frail patients. In general, if you ask your patients, most even frail, they prefer to come one week, 5 times than five weeks, once a week. And also, for scheduling it's often easier. And for locoregional limit fraction size for up to now to below 3 Gy. Re-irradiation, I have a lot of experience with re-irradiation because I worked in a hypothermia centre before, I favour strongly 40 Gy in 15 in 3 and not 25 fractions of 2, not 25 or 28 of 1.8. We know that 40 Gy in 15 is more gentle and as effective. So, we are too early to use 26 in 5 fractions in one week for re-irradiation, but moderate type of fractionation, perfect. And for everything I said, START with target volume definition and contouring, and also this has nothing to do with the fractionation. So, what with 50 in 25 in 5 when combined concurrently with radio-sensitisers, for example, with hypothermia? The Dutch protocol is 23 fractions of 2 Gy, five weeks with a weekly addition of hypothermia. Squamous cell carcinoma, extremely rare, but I just very recently treated another case. Then, we give weekly cisplatin just like in cervical cancer. It's a strong recommendation, A, but the level of evidence is forced. It's so rare that there is no quality data, triple

negative, locally advanced progressive disease under primary systemic therapy, combined radiation therapy, 25 fractions of 50 with capecitabine. We have a little bit more data level of recommendation, B, not as strong as with this SCC where we are really with our backs against the wall; BRCA, locally advanced progressive disease under primary systemic. Also here, III, B, with PARP inhibitors. There are some studies ongoing, and the first data are encouraging. And else? It's very easy. It's completely historical. So, for me, I don't call it... conventional, for me is 40 Gy in 15 fractions in three weeks and 50 Gy in 20 fractions for me is historical fractionation. And this has been confirmed in the ESTRO Consensus recommendation, where many of us also, Ivica, contributed to. And here, you can see for whole-breast irradiation, Ultra-hypofractionated can be offered a standard of care. Some countries are reluctant, they want to do more prospective randomised trials or prospective registration cohorts, identical for chest wall, not for nodal. Yes, for partial breast. Patient selection is updated and a fractionation. So, my bullet-points, level of evidence in favour of Ultra-hypofractionation's sufficient for patients are practise changing, no clear indications for breast, chest wall and partial breast, most arguments used for not using it a standard of care or not directly related to fractionation and the radiobiology. And we should focus our research or invest in Ultra-hypofractionation combined with immediate breast reconstruction, what to do, Pierfrancesco, with the boost in preoperative radiation therapy and in combined modality and nodal radiation therapy. And this is an advertisement, I add a book that will be published this month, that many of you contributed to and it's edited by two of my close friends and myself. So, those I would like to thank for the contribution, and this was the last slide. Final questions?

Dr Ratosa: Thank you very much, Professor Poortmans, for this very nice overview for Ultra-hypofractionation. Do we still have time for the questions, Pierfrancesco, or we are?

Prof Franco: We can. Five minutes, I think, it's fine.

Dr Ratosa: Maybe, a question, we don't have a question from the audience, but I have one question that for some patients now we see for patients with early breast cancer, some patients are candidates for partial breast irradiation, or whole-breast, right? And it's sometimes not so easy to decide, especially if patients with luminol cancers do not receive endocrine therapy. So, should we treat them with whole-breast with 5 fractions or partial breast? Of course, the less, the better probably because we have similar local recurrence rates, but maybe. what's your opinion on that?

Prof Poortmans: If you select your patients well, then, you will not impact an overall survival for the reason that's very easy, that's the impact an overall survival will take so much time that it will not be visible. So, if you start doing this in patients from age 50 years on, then, I'm afraid that after 20 years you will see a difference in overall survival. But if you select them also based on life expectancy, and especially, if you stay on the safe side and take it up to 10 years, we have enough data to say no impact on overall survival. Then it's local control. How important is local control? If you give both systemic therapy, hormonal therapy, and radiation, there are virtually no local recurrences. If you give either the hormonal therapy or the radiation therapy, the local recurrence rate at 10 years is way below 5%. In the most recent studies it's even around 1%, but then, we come to quality of life. And I have a lot of patients on follow-up who have huge complaints due to endocrine therapy, to hormonal therapy. And I have much less patients on the follow-up who have complaints due to surgery or radiation therapy. And that's the question for the EUROPA trial, which is managed by Icro Meattini and his group and that we will participate to starting in, I hope, at the latest, autumn this year. And there, the randomization is for the low-risk luminal A 70+ either endocrine therapy for five years or radiation therapy. And after the new amendments, the radiation therapy can also be whole-breast irradiation. It does not necessarily need to be partial breast because that was one of the components that made it a little bit more tricky. We will also have experience from the Dutch, the Dutch have for example, the TOP-1 study, the Netherland is one of the few countries in which the low-risk patients, standard, routinely do not get any systemic therapy, even of Tamoxifen. So, they also omit radiation therapy, that means that they are collecting a large cohort of patients who receive nothing at all. And if you look at the studies that

have been done investigating this, like BASO II and the yolk study, then, you see that if you don't do anything at all, you have 20 to 30% local recurrences at 10 years, maybe, with better patient selection, this will go down, but we have to wait for those data.

Dr Ratosa: Thank you very much.

Prof Franco: So, Philip, I have a very quick question for you. Can we use the 5 fractions for nodal irradiation yet, or probably not yet?

Prof Poortmans: No, we have there a lot of challenges. The FAST-Forward nodal has been presented at ESTRO for the three years side effects and was identical to FAST-Forward, no increased level of side effects with 26 in 5. However, the follow-up is still too short. And secondly, these are less than 500 patients. So, this is in contrast to FAST-Forward breast, chest wall only with more than 4000 patients, this cannot be considered as a level-1 evidence. So, we will need more studies evaluating the Ultra-hypofractionation for nodal radiation therapy. Moreover, they did not include the internal mammary lymph nodes. So, that's another study we are preparing in several circumstances, similar to the SIB with Ultra-hypofractionation to include internal mammary lymph nodes with 26 in 5.

Prof Franco: Great, thank you. Thank you, Philip. I think there's a last question from the audience about follow-up. Do you think that follow-up in breast cancer patients will change? So, it's five years enough? Because there seems no change after five years. I think he was referring to the, let's say, stable rate of adverse events from the 5 to 10 years.

Prof Poortmans: We had a very nice debate about the value of follow-up at ESTRO, where it was do patients with high-risk breast cancer need follow-up, yes or no? And it's clear that there is a debate, but in general, the trend is rather to go for no, not to do too much treatment for follow-up. For me, it's just after breast cancer treatment, five years, and annual mammography, then, every two years till the age of 75-point, that's everything that is evidence-based, all the rest is proven not to be useful. And that's something else, they're not proven to be useful. It's also one of the big differences between the Netherlands where only is done, what is proven to be useful. So, patients never have blood examinations, never have bones scan, never have... unless they have complaints. They have reason to do so, but otherwise, it's not routinely done. When I had in the early '90s a patient I invited for the boost, no-boost trial. And she said to me, "I fully understand the study. I don't want a boost." Okay, it was her wish, so I noted in the file patient have preferred no boost and no participation to the trial. And after the radiation therapy said, "Very happy with treatment, Dr Poortmans, if once in my life will have any issue, I will contact you, and if not bye-bye, I don't go to the surgeon, I don't go to anybody. I just take care, I have every year my mammography and once five years pass, two years." And I said to the patient, "You're right." This is from the early '90s, this is nothing new. And I'm still convinced that this is the best approach. If the patients don't have any issues, don't have complaints, why should we do this follow-up? We're doing much too much.

Prof Franco: Yeah, and of course, it's costly, time-consuming, demanding in terms of resources, so yeah.

Prof Poortmans: And there's so many funny things do in our job. We should focus on that. Not on follow-up. And also, the patient every year is stressed to come for follow-up. How are you? How is my mammography and my blood exam, A blood exam? Why did you do a blood exam? Yes, because the gynaecologist asked.

Prof Franco: The markers, yeah. It's an extra burden.

Prof Poortmans: Yeah.

Prof Franco: Yeah, so thank you very much, Philip. So, Ivica should we close?

Dr Ratosa: Yes, I think it's time to close. So, thank you very much for taking the time and for this wonderful presentation and answering all the questions, I believe that there are many, many questions to be answered in the future, so. Definitely, it's a challenging time, I think.

Prof Franco: But it's fun also, so, we need to work on that. So, thank you very much. And thank you, Philip. Thank you, Ivica, and thank you everyone for watching.

Prof Poortmans: Thanks a lot, bye-bye.

Dr Ratosa: Bye-bye.