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Re-irradiation in breast cancer

Dr Marta: So, first of all, thank you for the invitation. It's a pleasure to be here and talk about re-irradiation in breast cancer patients. I don't have conflicts of interest to declare for this presentation, and my talk will be divided in four items. One, introduction, considerations about second breast-conserving treatment, chest-wall recurrence and re-irradiation, and finally, conclusions. Remember, colleagues, that we can ask questions and send comments at any time. Please click on the Q&A button to send your questions and comments. Let's move to introduction. Radiotherapy is integral part of breast-conserving treatment. After lumpectomy, post-operative radiotherapy is related to improvement in any first recurrence, breast cancer death, and any death. Equally, for locally advanced breast cancer patients that underwent mastectomy and axillary resection, post-operative radiotherapy is associated with improvement in locoregional recurrence, in first recurrence, and breast cancer mortality. Historically, the ipsilateral breast tumour recurrence can occur in both breast-conserving therapy and mastectomy in 10 to 20% of patients. It is important to recognise that due to better diagnostic tests, local and systemic therapies, the risk of recurrence is lower nowadays. The Young boost trial demonstrated only 1.8% of local recurrence at nine-year. So, over the last 20 years, we observed down to 10, to 15% of recurrence. However, the number of breast cancer survivors will increase by 22% until 2030. These data come from US SEER database that we can also apply for different parts of the world. So, in this context, probably, more patients will develop ipsilateral recurrence and probably, more patients will need a second treatment, including re-irradiation. The decision to do or not re-irradiation should be balanced between side effects, and tumour control, and quality of life. re-irradiation together, surgery and systemic therapy is the treatment option for in breast relapse disease. And we need to select, well select patients based on tumour and patients' characteristics. The decision of re-radiation needs to consider, one, localization of the second tumour in relation to the initial radiotherapy volumes, and two, the previous exposure of organs at risk. Parameters of initial radiotherapy considered dose, fractionation, and volumes. Combination treatment of the first tumour, chemotherapy and biologicals, and time-interval from the treatment of the first tumour with regard to the potential tissue-specific morbidity at re-irradiation and its impacts on patient's quality of life. One important aspect related to re-irradiation is that different techniques can be used for this treatment. It's important to highlight that the largest experience comes from brachytherapy, but also, other techniques including external beam radiation can be used for re-irradiation. Nevertheless, the clinical indications for re-irradiation techniques, ideal dose, fractionation schedules have not yet been clearly defined. Another important component of re-irradiation is the hyperthermia. Hyperthermia is a radio-sensitizer that increases tumour temperature, decreases intratumoral hypoxia, and reduces sublethal damage repair in the tumour cells. And this is the ultra- summarizes results from five randomised controlled trials. In general, the overall complete response was higher in a group that received a combined treatment with re-irradiation plus hyperthermia, 59% versus 21% in the radiotherapy alone. And in this systemic preview and meta-analysis, the authors include 34 studies. And again, the final result demonstrated that complete response is higher in a combined treatment, involving radiotherapy

hyperthermia versus radiotherapy alone. And this is the end to assess the impact of hyperthermia thermal dose in retrospective data that included 120 patients. The patients were divided in two groups, the low and high thermal dose. The high thermal dose group had higher local control compared to low thermal dose group and no difference in overall survival in grades three and four late toxicities were observed between the groups. Again, colleagues from the audience, remember that you can ask questions and send comments at any time. In this scenario, what is the best evidence for re-irradiation? Let's move on to the second breast-conserving treatment. Many authors described the results of mastectomy and lumpectomy without radiotherapy after local recurrence. In general, the rate of second local recurrence after mastectomy is around 10% and after lumpectomy without radiotherapy is more than 20%. It means that probably it makes sense to add post-operative radiotherapy to improve this outcome. This table summarises the results of several studies in this scenario. All partial breast irradiation was performed using brachytherapy. Different techniques were used with different dose, and the risk of grade three or more toxicities ranges from zero to 17%. And globally, the rate of second recurrence after lumpectomy plus brachytherapy is around 10%. There is an important study, it comes from GEC-ESTRO group that assesses the results, the results of patients that receive salvage mastectomy versus second conservative treatment for second ipsilateral breast tumour event. In these studies patients from seven European countries were included. Patients were offered mastectomy or lumpectomy plus brachytherapy. More than a thousand patients were included, but in the final, 754 patients were met by propensity score. The propensity score was calculated with logistic regression and multiple imputations. Matching 1:1 was achieved using the nearest neighbour method, including 10 clinical and pathological data related to the second breast event. The following characteristics were included: age, time length between the primary and salvage surgery, salvage surgery period, tumour size, histological type, histological grade, hormone receptor status, HER2 status, endocrine therapy, and chemotherapy. The primary endpoint was five-year overall survival. And second endpoints were five-year cumulative incidence of a third breast event, regional relapse and distant metastasis, and disease-free survival and specific survival. As you can see here, no difference in overall survival, incidence of third ipsilateral breast tumour event, and incidence of regional relapse were observed between the groups. Moreover, no difference in incidence of distant metastasis, disease-free survival, and specific survival were observed between the groups. For patients that receive second conservative treatment, most often, developed grades one and two toxicities, only 8.8% developed grade three toxicity, and two patients developed grade four toxicity. This is another important GEC-ESTRO study that reports the results of 217 patients within breast tumour recurrence that underwent salvage lumpectomy followed by brachytherapy. 51% of the patients had initial tumour bed the site of the recurrence. Median does was 56 Gy, and most patients received high-dose rate brachytherapy. The median follow-up from the recurrence was 3.8 years. 9 patients developed second local recurrence and 22 patients developed distant metastasis. And this figure, we can see the site of the second recurrence with primary tumour in red, first recurrence in blue, and second local recurrence in yellow. Five-year overall survival for all patients was 88% and 10-year overall survival was 76%. Patients developed side effects including, cutaneous and sub-cutaneous fibrosis, telangiectasia, hyperpigmentation, and ulceration. But 89% of patients developed grade one and two toxicities only. And regarding cosmetic assessment, all patients considered, most of patients, sorry, are considered excellent or good cosmetic results. Another technique available for re-irradiation is intraoperative approach. This table summarises some evidence for that, but it's important to mention that a linked number of patients were included. The majority of patients were treated with 20 Gy and the risk of recurrence ranged from zero to 10%. And the probability of grade three or more toxicity ranged from zero to 21%, depends on the author. Again, colleagues, remember that you can ask questions and send comments at any time. Another technique available is external beam radiation. In this table, we can see some results about this technique in re-irradiation scenario. It's important, again, rely that a limited number of patients were included with different techniques. The local recurrence rates ranged from 5 to 14%, and the probability to develop grade three or more side effects ranged from zero to 16%. In this context, this study is very important to mention. RTOG phase-II trial that included 58 patients with in-breast recurrence, tumours up to three centimetres, one-year or more after initial treatment unicentric tumour,

and no skin tumour involvement. All patients received salvage lumpectomy followed by external beam conformal radiotherapy. 1.5, twice a day radiotherapy in a total dose of 45 Gy was used in this protocol. The median time from previous radiotherapy was treating years. And as a result, five-year in breast recurrence was 5.2% and five-year overall survival was 94.8%. Four patients developed in breast recurrence. Two inside and two outside the treatment field. Almost 50% of patients developed grade one and two side effects, and only four patients developed grade three toxicities. Grade four and five toxicities were not reported in this study. Based on the available data that I mentioned, what is the best partial breast irradiation technique for re-irradiation? The correct answer is that we don't know, because a technique uses different dose, and the philosophy for target followed is different based on the used technique. So, it's harder to know the best approach for this scenario. For colleagues that decide to use external beam irradiation, this table can help in the clinical practice. The normal tissue constraints used in RTOG and in all trial is summarised in these tables. Let's move to the chest-wall recurrence. After chest-wall recurrence, most patients receive second surgery resection, but after surgery alone, the risk of recurrence is higher. Maybe, almost 70% of patients will develop a second tumour recurrence. It is important to recognise that systemic therapy after local treatment can improve outcomes. In this study, patients with isolated locoregional recurrence received mastectomy or lumpectomy with clear surgical margin and were randomised to receive chemotherapy or no-chemotherapy. Chemotherapy was related to improvement in disease-free survival and overall survival for all patients. However, 15% of patients developed serious adverse events, and only 19% of the patients were treated with re-irradiation in this trial. There are some data to support the re-irradiation for chest-wall recurrence, but again, different modalities can be used in the practice. A limited number of patients were included with different doses, and the local control ranges from 50% in two years to 75% in three years. And the risk of side effects ranges from 7 to 6%, it depends on the authors. So, in the clinical practice re-irradiation cannot be considered a standard of care, but we can consider based on well-selected patients, including characteristics in prognostic factors, time interval from the treatments, side effects of the primary radiotherapy. So, re-irradiation to chest-wall can be considered for macroscopic disease if surgery is not feasible. For microscopic disease after resection, And for microscopic disease after systemic therapy. There are different scenarios in this approach; in the section one, patients that received a complete resection without risk factor, no re-irradiation, just a follow-up. In the section two, after complete resection with risk factor, we can consider re-irradiation if no other or controlled disease, favourable tumour biology, long-life expectancy, no or limited side effects. Sorry, from the earlier radiotherapy. In the setting three, microscopic incomplete resection. We strongly consider re-irradiation if no other or controlled disease in favourable tumour biology, long-life expectancy, no or limited side effects for early radiotherapy. And finally, in the setting four, microscopic incomplete resection, we could strongly consider re-irradiation if no other controlled disease, in favourable tumour biology, or expected, or symptomatic disease. Again, colleagues from the audience, remember that we can ask a question and send comments at any time. In conclusion, locoregional recurrence rates after radiotherapy for breast cancer went down a lot, but breasts cancer survival will increase in the next years. It's important to assess carefully physical, physiological, and radiobiological parameters of past radiotherapy. Re-irradiation is often indicated as component of curative intent to treatment. Hyperthermia can improve outcomes. And second breast-conservative treatment, including surgery plus partial breast irradiation can be considered standard for selected patients, unicentric without a skin involvement, isolated recurrence, no concurrent regional distant relapse. Tumour size up to three centimetres. Preferably, time between the first and second treatment, more than three years. A multidisciplinary tumour board is important to individualise treatment approach. It's also important to recognise that systemic therapy added to adequate locoregional treatment can improve survival. And further prospective studies are required to evaluate this second tumour, lumpectomy plus re-irradiation versus mastectomy and re-irradiation for chest-wall recurrence. Including the assessment of the best technique and treatment dose for re-irradiation. Remember, no randomised phase-III trials to support the second breast-conservative treatment and re-irradiation after salvage mastectomy are available to support our practice. I'd like to thank for your attention, and thanks to my colleagues, especially to Dr Philip Poortmans, Icro Meattini, Orit Person, and Pierfrancesco Franco. Thank you very much.

Prof Franco: Yeah. Thanks a lot, Gustavo, for this excellent overview on this very, very intriguing topic. So, thank you. Thank you very much. I think we can open the discussion. Maybe, Ivica, you can start. You want to start? I think there's a question coming from the audience.

Dr Ratosa: Yeah. Thank you very much for this very nice presentation. Yeah. We have already two questions from the audience. And one question is about the dose with the second course irradiation. So, what dose would you recommend in case of chest wall recurrence with positive margins? So, for patient that underwent resection with the positive margins. So how do you take into the account previous dose and what would you recommend? According to.

Dr Marta: That's a very nice question. It answers depend on the technique that the colleague we use for that. As I show different protocols, is different protocols are used in the clinical proxy. My own experience is used, for example, one, instead of re-irradiation, I have some patients treat with conventional dose and more recently, with can hypofractionated dose. I know that hypofractionated is not well studied in this scenario, but I use this schedule in my proxy for select patients. I don't know if refers for Pierfrancesco. I have a different approach for this situation.

Prof Franco: So, yeah, my other question to you was, and it's kind of linked to this question. So, do you use like different dose and depending on the residual disease that you have, let's say macroscopic disease, or microscopic margin, or no margin at the resection? So, would you somehow stratify the dose you give to the patient depending on the risk? And of course, this has to be somehow counterbalanced by the proximity to organ at risk, the background dose that the patient received during the first treatment. So, of course, at first you do what you can do depending on what has been done before and depending on the anatomy of the patient and the location. But let's say theoretically, in an ideal scenario where you could differentiate the dose, would you differentiate the dose or would you stay on a standard dose depending on the macroscopic, microscopic, or no residual tumour?

Dr Marta: Maintenance is, try to prescribe a higher dose for macroscopic disease. But again, we need to consider different aspects and analyse if safe or not prescribe a higher dose and for this specific patient. Okay? But I think that's for select patients, dose is important issue, but re-irradiation in general is also important issue. I prefer to prescribe secure a dose that is related to a safe treatment instead of no treatment re-irradiation treatment.

Prof Franco: So yeah, you say if you, if your dose would be suboptimal because of the previous treatment, but still you would go for radiation compared to no radiation.

Dr Marta: Yeah.

Prof Franco: Which is…

Dr Marta: For select patients, for sure.

Prof Franco: Which is sensible. And Gustavo, you're talking about conventional fractionation. So, you say you would go up to 50 Gy conventional fractionation?

Dr Marta: 50 Gy. Yes. For clear margin, 50. And I have some experience with 60 Gy. It's a, it's experience that we have for boost patients. Okay?

Prof Franco: Okay.

Dr Marta: But as I mentioned, I also have some previous experience with interpretative with electron beams that we can prescribe 20 Gy for re-irradiation scenario.

Prof Franco: Okay. And Gustavo, you mentioned about hypo, that you use hypo for re-irradiation. Are we talking about mildly hypofractionated schedule, like the UK or Canadian fractionation?

Dr Marta: The UK philosophy first, yeah. The UK philosophy. And...

Prof Franco: So, it would be 40 in 15 fractions? Okay.

Dr Marta: Yes. Yes. Perfect.

Prof Franco: And then, sorry?

Dr Marta: And I'm thinking... and I'm thinking to try to prescribe a new philosophy about it. It's why we cannot think about to prescribe fast-forward philosophy for re-irradiation. I know, there's no data supporting this approach, but when we analyse results of brachytherapy patients, the similar biological dose is prescribed. So, why not to use this, in clinical practice for selected patients?

Dr Ratosa: I have also another question. Since most of the toxicity, let's say, late toxicities are related to the skin, subcutaneous tissue. Also, some ribs, necrosis is possible. Do you have any extra recommendations in treatment planning process regarding dose to the skin or subcutaneous tissue or ribs, or you don't take this into the account?

Dr Marta: It's important to analyse the preview treatment. The dose that was preview previously offered for the past patients, and performed a technique that they covered, the partial breast volume, and with homogenous dose to avoid high risk of side effects. But as I showed, the risk of grade three or more toxicities is quite lower compared to grade one and two toxicities. We can consider results of JRO group, most of patient developer grade one and two toxicity only. It's not to manage in our clinical proxy.

Dr Ratosa: Okay. Thank you. I think we have another question, another question in the chat. Pierfrancesco, would you? So, it's the third question.

Prof Franco: Yeah. This is about, like…

Dr Ratosa: About…

Prof Franco: The case, the scenario of breast conservation. So, second breast conserving surgery and re-irradiation with a partial breast irradiation. So, and the question is about dose. What kind of dose fractionation would you advise? But I can somehow complement the question, because, so, in this scenario, we want to re-irradiate, then we would need to partially re-irradiate the breast, right? So, we will go for partial breast irradiation, either with multicatheter brachy, or external beam, or IORT, it's all partial breast irradiation. But we know that from, like, the primary treatment that we use partial breast irradiation for selected cases, right? Small tumours, favourable intrinsic subtyping, N0. So, I'm okay in using partial breast irradiation for a second ipsilateral breast tumour recurrence, or second primary for a luminal case. Like, let's say, 20 years, local relapse, I'm fine. This is the same scenario where I would use partial breast irradiation in a primary treatment. But let's say, we have a second tumour or a recurrence of an unfavourable biology tumour like, let's say, triple negative breast cancer or also a tumour with some other risk factor, like vascular invasion or grade three. So, like, those factors that you would not prescribe theoretically partial breast irradiation. But then, you are in a scenario of re-irradiation so, you cannot re-irradiate the whole breast theoretically, and you would go for partial breast irradiation. So, is it like a safe type of treatment, or we still need to stick to those selected patients where the criteria for a partial breast irradiation as primary treatment would apply?

Dr Marta: Well, it's a good point, Pier. I think that for re-irradiation we need to be more restrict. I do like to offer, for example, a second whole breast irradiation for very high-risk patients. You know the history about partial breast irradiation for high-risk patients, but in this, there's a second course of radiotherapy. And again, we need to balance between the side effects and the outcomes, the local control. And in this scenario, we cannot forget that systemic therapy can also improve local control for these patients. So, it's not easy answer. There's a reason that a tumour board discussion is very, very important in this context.

Prof Franco: Yeah, I think it's a good point, Gustavo, because sometimes we are referred patients without having been discussed. So, the patient gets a second breast-conserving surgery, and then, we might be in trouble in re-irradiating the patient. So, it doesn't make any point to offer patients with breast conservation if we cannot offer a second course of radiation, because these patients will have a very high-risk of local relapse, 20, 30%, depending on the characteristics of the relapse. So, I agree with you. It's very important to have...

Dr Marta: For example, are you comfortable to offer a second course of whole breast irradiation for recurrence of patients in your practice?

Prof Franco: I never did. I never did. I don't know if Ivica you did, and Gustavo, did you do that?

Dr Marta: No.

Dr Ratosa: No.

Dr Marta: No, no. Yeah. It depends.

Dr Ratosa: Only partial. Yeah.

Prof Franco: Yeah.

Dr Marta: Yeah. There's a point. Yeah.

Prof Franco: Yeah, but because, yeah, I see. But if you select well the patient, and we see from the data that you showed the RTOG 1014 patients, I think that the risk of ipsilateral breast tumour recurrence, there was like around 5%, but this was, there were very well selected patients with very small, small relapse, like good intrinsic subtyping, good biology, no skin involvement. And so, but that's a good message that the second breast-conserving therapy is feasible and the results are very good. If you properly select the patients, as always in medicine and irradiation and in oncology.

Dr Marta: Yeah, yeah. For sure.

Dr Ratosa: So, ideally, all the patients would be presented at MDT meeting to discuss all the options and to see if there are any side effects from the previous radiation treatment. So, yeah. As you said, Pierfrancesco, it happens now from time to time that patients are getting second breast-conserving surgery before, let's say, consulting traditional oncology first, so department, so it's sometimes, yeah, hard to decide what dose and volume is going to be treated with the second radiation course.

Prof Franco: Yeah. And, but I think we missed the question from the audience. So, Gustavo, for this scenario, PBI after second breast-conserving surgery. What dose in fractionation would you use? Of course, it would depend on the technique, I guess, again.

Dr Marta: It would depend on technique. But in my practice, I have three options. First, external beam radiation conventional dose. Second, hypofractionation, moderate hypofractionation. And I had some experience in intraoperative IORT, intraoperative approach with electrons with 20 Gy. This is my experience. I don't have any experience with brachytherapy for re-irradiation patients.

Prof Franco: Which is however, a very nice technique because multi-catheter brachy, if you have the facility and then you have the person who can do it, you get a very, very nice dose distribution with this, so.

Dr Marta: Yeah. Do you guys have experience with hypothermia approach with re-irradiation? Because I don't have an experience with re-irradiation with hypothermia.

Dr Ratosa: I don't have experience. I don't think there are many centres that have this experience.

Prof Franco: No, no, not. I mean, at least not in Italy. I mean, like Switzerland, there is like a good experience, Germany also.

Dr Ratosa: Netherlands.

Dr Marta: Netherlands, yeah.

Prof Franco: In Switzerland is reimbursed, so. But that would be mostly for chest-wall. I agree. I wouldn't see it for the second breast-conserving surgery.

Dr Marta: Yeah, yeah. Just, yeah, yeah, yeah. You're right. Yeah.

Prof Franco: Yeah. It's good.

Dr Ratosa: I think there are no more questions from the audience. No.

Prof Franco: No? There are no more questions. Gustavo, I have a... you mentioned about that, so let's go back to the chest-wall re-irradiation. So, recurrence after a mastectomy, chest-wall re-irradiation, you mentioned about risk factors, right? So, patients having no risk factor or a patient having risk factor that would increase, let's say, the likelihood for to receive a second-course of radiation. What are the main risk factors that would push you to prescribe re-irradiation?

Dr Marta: The size tumour, the size tumour, the grade three tumour, triple negative tumour, and vascular invasion, pleural invasion. So, the classical risk factors, I think that we can also consider for re-irradiation.

Prof Franco: Great. Is skin involvement? Because I see one of the exclusion criteria, I think, in the RTOG 1014 was skin involvement, which is considered a risk factor. So, I mean, because I would think, I would include the patient with skin involvement if the skin is removed, then I would re-irradiate because they're higher risk, but in the trial, they excluded those patients.

Dr Marta: They exclude those patients. I think select well patients for re-irradiation and have good results. But I agree with you. In general, after resection, why not to include skin involved mutations. Could be a good option. But again, I think that's very important approach to discuss these patients in multidisciplinary tumour board.

Dr Ratosa: What about concomitant chemotherapy with second radiation course, following chest-wall recurrence? I had one patient with a HER2 positive tumour that was on T-DM1. Would you in this case consider or change your fractionation schedule, or would you give, systemic treatment concomitantly, or discuss this with medical oncologists since there are no data about this approach?

Dr Marta: Yeah. I'm afraid with concomitant treatment because the toxicity that we don't know exactly what will happen with the patients, and my tendency is perform first, re-irradiation and then follow to chemotherapy or systemic therapy approach. I'm not so comfortable to do both treatments together. And on my site, I can try to use some techniques to improve the time, for the second time, of re-irradiation include, for example, intraoperative approach.

Prof Franco: Yeah. The other consideration is, sometimes, that you think that you're not doing concomitant, but normally, to define a concomitant treatment or not a concomitant treatment you need five halves-time of the drug. And for some drug, the half time is very long. So, even if you wait for a couple of months and you think you're not doing concurrent, but actually, you are doing concurrent.

Dr Marta: Yeah. Yeah. It's another point. You're correct. Yeah.

Prof Franco: Yeah. Is there any role for protons for you in this setting or not at all?

Dr Marta: Well, there are some data that use proton therapy for re-irradiation. It's also a technique available, but I don't know if, I don't think that we need protons for re-irradiation is the first point. The second point is, protons are limited worldwide. And the third point is that the biological dose distribution can also be good for other techniques, including brachytherapy, intraoperative, and also photons. So, in my opinion, proton is not mandatory in this scenario.

Prof Franco: Yeah. It could also be challenging because of the skin dose, right? Which is higher.

Dr Marta: Yeah.

Prof Franco: So.

Dr Marta: Yeah, and this is another point.

Prof Franco: Great! Great, great. I don't see any further question from the audience.

Dr Ratosa: Okay.

Prof Franco: Elisa, do you have any burning other question?

Dr Ratosa: No, I think we have...

Prof Franco: I think we'll stop the call.

Dr Ratosa: Yeah.

Prof Franco: Yeah.

Dr Ratosa: We covered everything, almost.

Prof Franco: Yeah. So, thank you very much, Gustavo. And thank you very much, Ivica, for the very nice session, and thank you all the attendees for joining us, and have a lovely evening.

Dr Ratosa: Thank you.

Dr Marta: Thank you so much for the invitation. It's a pleasure. And again, I'm so sorry for my problems in the beginning.

Prof Franco: It's okay. No problem at all. Bye-bye.

Dr Marta: Bye-bye. See you.

Dr Ratosa: Bye-bye.