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RT in breast cancer patients after breast reconstruction

Dr Kaidar-Person: Thank you so much for inviting me and it's a big pleasure for me to participate in the session. And remember, as it was told in the video, we encourage you to ask questions and participate. So, I'll be talking about radiation in breast cancer patients after breast reconstruction. I have no conflict of interest. I'm a radiation oncologist, a full-time clinician. So, I'm speaking from experience in treating these patients. And I'm currently a foreign PhD student at MAASTRO, and my research is focusing on improving the outcome of breast cancer patients who undergo mastectomy and breast reconstruction and our plan for post-mastectomy radiation. So, part of my talk will be from data that we gathered doing my research work. I will try to cover new challenges that we encounter as radiation oncologists and what we can do about it when we treat these patients. I will not cover in this talk, but it's very important the indication for postmastectomy radiation, the results of the EBCTCG update in 2014, and how we changed our insight about postmastectomy radiation. Postmastectomy radiation versus breast conserving therapy, there are quite a few interesting publications with regards to efficacy and other many important topics with related to mastectomy and postmastectomy radiation. And again, we encourage you to ask questions because this talk will be much better if we interact. So, the rate of mastectomy and immediate breast reconstruction is increasing. Whether it's patient wishes, surgical techniques improved, then, it's much easier and accessible, whether it's less fear from combining it with radiation, we have quite a lot of data. Why are we seeing these trends? In some cases, it's even related to what is called the Angelina Jolie effect, in 2013, when she shared with everyone that she's a BRCA carrier, and the number of patients who underwent even prophylactic contralateral mastectomy as a result from this statement increased or even tripled the number of these patients. And parallel to that, we see that the rate of postmastectomy irradiation is increasing. And we mainly attribute that to the 2014 results of the EBCTCG meta-analysis that even showed that post-mastectomy radiation in patients who underwent mastectomy. And I'm talking about modified radical mastectomy, total mastectomy with axillary dissection, post-mastectomy radiation in patients who had one to three lymph nodes was found to reduce local regional recurrences and improve breast cancer specific survival. This was one of the reasons that we see an increase in the number of patients who undergo mastectomy and are referred to post-mastectomy radiation. But this is not the only reason, we know that currently the axillary management in patients with clinically node negative but pathologically node positive, or after primary systemic therapy is quite different between countries, but there is a tendency to de-escalate axillary surgery and refer those patients to postmastectomy radiation. So, this is a study that was published in 2015, but these trends are constantly increasing. And this reported that the immediate breast reconstruction with implant only increased from 27% to 52% with the decrease in immediate reconstruction that is based on tissue only that is autologous-based reconstruction and immediate breast reconstruction rate among patients who need radiation has increased as well. And this slide also is relatively old, but this is the nicest

illustration. We have more recent data as well showing the same trends, but I think this figure demonstrate really nicely, which type of reconstruction is done, as you can see here, the rates of tissue only autologous-based reconstruction is decreasing over the years while there is a constant increase in the rate of implant only reconstruction. And of course, we see different trends in the rates of tissue and implant-based reconstruction. In some of the cases, there is an implant and also like in cases they transfer the latissimus dorsi, they can combine both tissue and an implant for the reconstruction. It is highly dependent on the surgeon and on the patient body habitudes and patient wishes. So, and specialty of the surgeon in some cases, the surgeons are more comfortable with an implant-based because it is a relatively easier procedure while an autologous procedure is a very delicate procedure and the patient is subjected to complication in the donor site and in the area of the reconstructed breast. And again, as we can see here, the trends of unilateral breast reconstruction, and there is an increase in the rate of bilateral reconstruction for a unilateral disease. And we should remember, and in this case, this is in breasts patients who are eligible for a breast conservation surgery. And that does not mean that these patients are not referred to post-mastectomy radiation. Because we need to remember that most of the indication for postmastectomy irradiation are because of node positive disease and high-risk features. So, these patients can also be eligible for breast conservation. But we also know that combining immediate reconstruction or even delayed reconstruction with post-mastectomy radiation results in poor outcome compared to patients who have reconstruction without radiation, mainly in cosmesis, but also, in other types of complications, necrosis and infections, in some cases. And in some cases, it may also result in poor disease outcomes. And there were some publications, I think the latest was in the "British Journal of Surgery" in 2020, that indicated the surgical complication after immediate reconstruction resulted in poor breast cancer outcomes. This study included 438 patients, and out of those irrelated to radiation, 27% had postoperative complications. These patients, in the patient group that had postoperative complication, resulted in 16.7% recurrences compared to 5.9 recurrence rate in patients who did not experience complications. And there are many reasons for that. So, it is very important that if you have a high-risk patient that you think that the oncology treatment is very urgent, this is the time to involve a multidisciplinary decision and decide whether the reconstructive surgery might compromise oncological treatment. Breast cancer, reconstruction, and radiation, we know we have bad results and in some cases. So, reconstruction failure occurs in approximately 20% of the patients with an implant. And there are less failures in case of post-mastectomy radiation in an autologous-based reconstruction. So, in this cohort, they were no autologous reconstruction failure, but some of the reports indicate that it's approximately up 4% of autologous failure in case of post-mastectomy radiation. We know that patients reported outcome satisfaction with their breasts and sexual well-being are lower in patients who undergo reconstruction with an implant compared to an autologous and need to go post and receive post-mastectomy radiation. But yet, as I shown you before, the trends of implant-based reconstruction are constantly increasing even though we know that we have poor results compared to an autologous. Both immediate reconstruction and post-mastectomy radiation resulted in high-rates of severe capsular contraction in implant-based reconstruction and in fibrosis in case of autologous breast reconstruction. So, some of the series, older series talk about approximately more than a third of the patients within an autologous, immediate autologous breast reconstruction and radiation have severe fibrosis, but with current radiation methods, newer studies report lesser rate of fibrosis of the autologous. So, I hope we have some questions in the chat. Can you check?

Prof Franco: Yeah, sure Orit. There is a couple of considerations, the first one is basically a comment like of one of the persons attending saying that radiation therapy, I would rather disagree is not a clinical specialty, but a kind of a surgical specialty. I don't know what's your take on it. I would say that I consider myself as a clinical oncologist and I consider radiation oncology as a discipline, pretty much clinical.

Dr Kaidar-Person: I hope the surgeons are also clinicians, so, I'm not sure of this definition. I would love to, if they can indicate in the chat what they mean as well, but we're sitting, and I hope in this talk, and I will try to be less formal maybe when I speak, I hope that you will agree that we need to participate in all the multidi.

discussions and we have a lot to say, and I hope I will convince the audience about that, that we are very much clinicians. And I would like to say, even detectives, because we need to decide where we want and how we want to irradiate.

Prof Franco: Yeah, and definitely treating patients requires being clinicians on a like-wider spectrum, so.

Dr Kaidar-Person: I fully agree, I fully agree.

Prof Franco: Yeah, and the second one is about timing, is a little bit about the timing of postoperative radiotherapy in post-mastectomy cases probably, but also in breast conserving surgery. If you have any comment on the right timing to indicate radiation for a patient.

Dr Kaidar-Person: I think this was the million-dollar question a few years ago. We had many studies trying either retrospective and I think from Yale, it was a prospective study, trying to understand the correct timing to reduce the complication-rate in postmastectomy radiation. And there were two systematic reviews published in 2014, one on autologous and the other one was on implant-base, trying to understand whether it's better to irradiate the chest wall and then do a reconstruction, or you can irradiate after immediate breast reconstruction. So, the complication rate is almost the same with regards to an implant-based reconstruction. Overall, the reconstruction failure was approximately 20%, but I think we made a significant progress over the years with regards to surgical techniques. And we can talk a lot about the different reconstruction techniques that improved significantly, but also with radiation, we know that we are much more aware of dose-homogeneity, volumes and dose in fractionation, and we significantly reduce the toxicity associated with radiation in breasts.

Prof Meattini: Orit, we received another question from the audience that is how about the timing of endocrine therapy. If you have a high-risk patient, would you consider starting the endocrine therapy during radiation therapy?

Dr Kaidar-Person: I love that question. I have a slide about that. So, maybe we'll go, this is a great question. And we constantly encounter this in clinics. So, if we move forward a bit with the slide, then, I hope I will be able to answer. So, I will continue now and then we'll address additional questions. So, again, we are clinicians and when we see the patients, and I hope that most of you, if not all of you are sitting at the multidisciplinary meetings, when they initially present the patient before the operation, because that what we are constantly doing and at the time of diagnosis of breast cancer, if it's possible, advice for breast conservation surgery. You can give primary systemic therapy, if that's the case, but these patients have better outcome. Remember even with the best reconstructive surgery and even if we manage to minimize the complications, some suffer from chronic pain syndrome, fibrosis, toxicity, recurrent surgery. So, if we can, it's better to maintain the breasts, if it's oncologically safe. This is what should drive our decisions. Consider the risk and benefits of post-mastectomy radiation prior to surgery consult with the surgeon, say, we will probably need to irradiate this patient. Are you sure you want to offer this patient breast reconstruction? Is she eligible for conservation? And identifying the cases that are prone for complication. And I will speak a little bit about that. Patients who smoke, we know that some surgeon even refuse to perform breast reconstruction in patients who are smoking. Patients who have comorbidities, especially, vascular disease, diabetes mellitus, these patients are prone for complication. Discuss with the patient and with the surgeon the surgical procedure, the difficult and be involved in the process. We review the imaging prior to the decision of surgery, and it's very important. And I will show you in my later slides, why is it important. Why it's important to take part at the time of diagnosis of breast cancer. So, what are the risk factors for complication after reconstruction and radiation? So, we can say that we have patient-related factors that we cannot control, some of them, like comorbidities, diabetes mellitus, smoking. I do advise my patient to stop smoking. This week I had a patient, in Israel we can perform, they do perform reconstructive surgery on patients who smoke, but we know that the outcome is very poor. I just showed the patient the CT that her lungs were terrible. They have to stop smoking. With radiation we also increase the risk for lung cancer. We should think

about all these components when we treat and decide about treatment for a patient. Body habitus, we know that patients with high BMI tend to have more complication with different reconstructive surgery. We know that these patients are also challenging for radiation. Sometimes, we have folds of subcutaneous on the chest wall that is also called dog ears from the professional side of the term. And these areas that are not flat, not homogeneous, are sometimes...they tend to have dose-homogeneity also, and tend to have more complications, skin complication in this area. Some patients have genetic susceptibility to radiation, and sometimes, it's the patient's desire who puts them at risk for complication. And I have a slide for that as well. We know that we have treatment-related factors, systemic therapy. So, I will address the endocrine therapy later, but we know that patients who receive chemotherapy have a tendency for more complication, the type of surgery, also, the expertise of the surgeon is also important, and the quality volumes dose in fractionation of the radiation therapy all are, these are complications for poor outcome in case of radiation. Patient's risk factors. So, we, I said a few things about the body habitus, but look at this about susceptibility to radiation. This is after breast conservation surgery, but patients with connective tissue disease who have chronic inflammation have a tendency to have poor outcome in the setting of radiation. This is one of the considerations that you need to take into account when you sit at the multidisciplinary meeting and advise about treatment. And this is an example for a patient desire. This is a young patient that had, she was eligible for breast conservation surgery, but she had a high-risk disease. We wanted to irradiate the lymphatics, including the internal mammary nodes, but she decided to do a bilateral mastectomy with immediate reconstruction. And as you can see here, the way the reconstruction was done, we were very limited with our ability to deliver radiation safely. So, we had to decide whether we want to irradiate the internal mammary node, or we wanted to either, if it's a field-in-field-based technique, then we had to go into the contralateral uninvolved breast. And when we tried all sorts of VMAT-based radiation, the lung dose, the heart dose were too high to treat her. So, this is one of the patient's desire risk, as a risk factor. And this is a case of poor selection for skin sparing mastectomy and immediate reconstruction. This is another patient of ours that was operated elsewhere. She had a multi-focal disease that's, as you can see in A, here, the foci, one of the focis were very near the subcutaneous, but it did not involve the skin. According to the pathology report, all the tumors foci that were known were taken out. So, the surgeon was very happy and thought that he did a great job. The patient had immediate reconstruction. She had complications with infection, and by the time she was referred for radiation therapy, this is the image, all the cancer recurred at the area of the subcutaneous. She doesn't have any distance disease. So, this is poor selection of a case for immediate reconstruction. And this is why you need to sit at the multidisciplinary meeting and help to decide who are the patients and how we treat them. So, again, advice breast conserving surgery, consider the benefits of postmastectomy radiation prior to surgery, identify the patients who are prone for complications, and discuss the surgical procedure as I showed you in cases that the tumor is very close to the subcutaneous, maybe, this is not the correct procedure. Be involved in the process. And what happens after surgery, before radiation, as a radiation oncologist, since now, with new radiation techniques, we have the ability to delineate the volumes, to do dose painting, to give a boost either we want to give a simultaneous integrated boost. And the way we delineate the volumes is highly important because it influences the dose to organs at risk. So, it's very important. And we neglected that so much in breast. We do it in anal cancer, we do it in rectal, in esophageal cancer, but we forgot to do that in breast because breast is supposed to be very easy. It's based on two tangentials and a third or a fourth field, that's it. So, no, it's no longer the case. So, you need to understand the type of surgery and reconstruction. You need to understand the extent of disease in the high-risk areas of recurrence. And I'm not talking about the indication of post-mastectomy radiation, I'm talking the area that you want. As a radiation oncologist, assure that you're covering this area correctly. You need to understand how to better define the target volumes. You need to understand the MR. You need to look at the state, the images that was done for staging, especially, in cases of primary systemic therapy, what are your radiation objectives as a radiation therapist? In some cases, I would agree for a lower dose in an area just to protect the heart. But if the tumor was medially, I would not agree for that. So, you need to adapt the objective of treatment according to the patient. In which dose and fractionation is better. I hope we'll have

a short discussion after that, and radiation technique to achieve your goals. You need to discuss and consider the pros and cons of each radiation technique. It doesn't mean that every new technology is the right technique to irradiate a specific patient. And when we look at the surgeries and we try to understand the new surgeries that are done, so, in case of skin sparing or nipple sparing, which nipple sparing always come with skin sparing procedure, the skin is conserved to create a pocket that will facilitate the immediate breast reconstruction. And in case of skin sparing mastectomy, the breast parenchyma needs to be accurately dissected from the covering skin at the level of the superficial fascia. So, here it's...as you can see, it's in light blue, the superficial fascia. So, the surgeon needs to go round this area and to resect the breast glandular tissue, but it's not easy to identify or perform. It's not like this nice figure. They don't always see, recognize where the fascia is. And it's very difficult, as you know, probably, that if they resect too much, they might harm the vessels that supply the blood to the skin and then, they won't be able to perform the immediate reconstruction. And there are different amounts of residual breast tissue and potential residual disease at different areas of the breast. So, if this is not done correctly, and there are quite a few papers about the residual breast tissue and the thickness of the skin flap that is left after skin sparing mastectomy, and I highly recommend that you go and read the "Skinny Trial", which evaluated the thickness of the skin flaps in case of immediate reconstruction. And this is one of our publications that we try to understand the areas that we have residual glandular breast tissue after mastectomy according to the type of the mastectomy procedure. And as you can see, in case of skin sparing mastectomy and nipple sparing mastectomy, most of the residual breast tissue is in the upper outer quadrant. We know from anatomy books, that this area in the native breast have more glandular tissue, but we also know and understand that part of the reason that we see more residual breast tissue in this area is associated with the surgical approach to perform these procedures and also, remember that axillary dissection is rarely or, in some countries, is rarely performed and in most cases is done as a sentinel or targeted auxiliary dissection. So, it's only natural that part of the breast axillary tail is not correctly dissected. And this is another paper that we published, that we try to map the spatial location of local recurrences after mastectomy. And as you can see here, most of the recurrences differ a bit when we speak about autologous-based reconstruction, A, compared to post-pectoralis implant-based reconstruction. And we don't show in this slide pre-pectoralis, which is now becoming more and more popular, but most of the recurrences occur in the subcutaneous tissue and in case of an autologous, the area of the subcutaneous of the native breast, because in some cases, some of the native breast tissue is...of the native breast skin is preserved. And this is an example, an additional patient we had, a recurrence at the biopsy tract after implant-based reconstruction without post-mastectomy radiation. So, how there are quite a few case reports about biopsy tract recurrences after skin sparing mastectomy. And then we asked ourselves, why are we not seeing it in breast conserving therapy? And the reason is that these patients in most cases receive radiation therapy. There is one report from the PAPBI Trial, it's a trial from the Netherlands about partial breast irradiation prior to surgery. And they did report cases of biopsy tract recurrences in low-risk patients. So, the area of the biopsy tract is a risk area for recurrences, and as radiation oncologist, you should learn about all the high-risk areas because these are the areas that you want to cover properly with radiation. And as I indicated before, the surgeons are limited with the ability to correctly resect the glandular tissue beneath the skin and the limits of anatomic extension may be imprecise. And this is a recent publication that we showed a few cases of recurrences after extensive DCIS. And as you can see, in the mammography, the DCIS went up, almost up to the subcutaneous. And you would assume that DCIS will be a safe thing for immediate reconstruction because DCIS is not an invasive tumor. You won’t expect it to go within the subcutaneous or to invade the skin, but these patients had early recurrence and when the pathologist looked at the slide, she actually saw the breast glandular tissue goes up to the skin, that in some cases there is no border like the surgeons think, or like it is written in anatomy books. So, the superficial margins in case of skin sparing mastectomy, and this same pathologist, she's from the Danish group, she also published about skip lesion of DCIS within the papule of the nipple in case of nipple sparing mastectomy. So, we need to act sometimes as detectives to understand where we might have residual disease. And I hope most of you are familiar with the ESTRO guidelines that were published about the volumes that we

recommend in case of immediate reconstruction. But I need to emphasize that these are consensus guidelines. These are not guidelines that are based on level-1 evidence, but are based on anatomical landmarks, literature review and some data that we gathered from different cohorts. The most important for you to decide about the volumes that need to be radiated is when you look at the patient before...the imaging before the surgery, understand the location of the primary tumor, understand where you might have residual disease, understand what type of surgery in the location of the implant is it pre-pectoral, post-pectoral, autologous, combined? and decide the high-risk volumes for recurrent disease. So, we can go back to some questions or continue with the talk, but I'm very curious to see if we have some questions because we had some wonderful ones before.

Prof Meattini: Yeah, Orit, thank you. We received a previous question from the audience. If there are studies for radio-induced tumors in case of autologous reconstruction? if you are aware of it?

Dr Kaidar-Person: Of secondary malignancy in autologous?

Prof Meattini: Yeah, related to radiation, yeah.

Dr Kaidar-Person: I haven't seen any and I'm very curious, so, I'm definitely gonna check now, it's a burning question.

Prof Meattini: No, no, okay. And thank you for having a light to the importance of the multidisciplinary discussion in the pre-and-post-operative setting. So, the existence of an active breasts units, basically, and I would like to receive a comment on why basically the autologous reconstruction rate is decreasing while a better safety profile is basically reported when irradiated. Did you think that is what you showed, the problem was surgical complication, or logistic reason, because are completely different surgery time and theater and so on, or do you feel that radiotherapy, modern radiotherapy doesn't fear anymore so much our colleagues? Just a comment.

Dr Kaidar-Person: I think you all, if I can choose all are correct. I would choose as a multiple-choice question. So, all of these are correct. So, we looked at some data before about the reasons and it's highly dependent also on the reimbursement setting. For example, in the U.S. it's much more financially beneficial to do implant-based. I hope I'm not recorded here, but also autologous based reconstruction needs a different specialty. It's a very delicate procedure and if there is a failure of the autologous you might leave the patient with no other option for reconstruction, depending how it's done. So, and you might have complication in the donor site and in the reconstructed breast. Additionally, I think some of it is associated with the patients. The patients, we see the same trends of breast augmentation increasing without breast cancer. So, I had in one of my previous talk I'm showing how the trends are really parallel, that the rates of breast augmentation is increasing. So, patients are feeling very comfortable with implants and so are the surgeons.

Prof Meattini: Thank you very much.

Dr Kaidar-Person: So, and how about planning? And this is very important because we radiation oncologists, we have a lot of tools, I hope at least that most of you have different kinds of abilities to irradiate in different methods. I mean, arc-based radiation to IMRT, inverse planning IMRT versus field-in-field planning. So, this is a study that we did that was initiated by the Danish Breast Cancer Group, and it involved all the centers in Denmark and a few other international breast cancer centers. And they were giving two cases, one of right breast cancer, one of left breast cancer. And the list of constraints according to the Danish Group for Breast Planning and we're told to plan radiation plans for a case of immediate reconstruction based on the new ESTRO guidelines. And as you can see, A is field-in-field based compared to B, which is a VMAT-based plan. So, in that publication, we describe the dosimetric differences according to the different plans. I think we had approximately 35 different plans. And for each type of radiation method, you have pros and cons. Different techniques can be used to treat a patient after immediate reconstruction. And from our study, we showed

that field-in-field provided a very good coverage with acceptable doses to organs and treats, and when you're using an arc-based and as you can see nicely from this figure, you need to decide about the trade-off between the target coverage and the organs-at-risk dose. And when you have a young patient, you really want a low-dose within the contralateral breast and with such volumes of the lung it's we don't have long-term data comparing secondary malignancies after these low doses in these patients. So, and we do have long-term data for fielding, not field-in-field, but tangential-based planning. So, this is something that as a radiation oncologist, don't use a certain method of radiation just because you have it. Play with it, see the doses, look at the dose distribution, look about the dose homogeneity. It's very important to make those decisions. And this is a slide about the dose and fractionation. There are so...there is level-1 evidence for hypofractionation, moderate hypofractionation in breast, but I chose...starting from the start A, start B, the Canadian trials. But I chose this recent trial from the Danish Group, and this is for the great question about endocrine therapy and radiation. And I chose this especially for that, to show you that in this publication by the Danish Group, they showed that the odds for a better outcome was in all cases better for the moderate hypofractionation even if the patient got chemotherapy, Trastuzumab, Letrozole, also for a different breast volume and even if the patient was a smoker. So, with the Letrozole, the odds for the moderate hypofractionation was least not as good as the risks, but if I have a high-risk patient that is planned for endocrine therapy, it depends on the case. I don't consider it as contraindication to give it concomitant with the radiation. It's highly dependent on the case of the patient. And as I said before, we have a lot of data about moderate hypofractionation. 15 or 16-fraction, and the better outcome with regards to toxicity to the breast, but it's most of the data, or it is about breast conserving surgery. We have little less evidence about chest wall irradiation and even less evidence about reconstruction, but we need to think about logic. If we irradiate the breast and the outcome is much better for this tissue, then why not in the setting of reconstruction? And this was voted in the St. Gallen as a safe fractionation in case of immediate reconstruction and also for nodal irradiation. And we have Professor Icro Meattini with us as a discussant, that is now working on the ACROP-ESTRO guidelines recommendation for fractionation in breast. And maybe, you would like to say a few things about that as well.

Prof Meattini: No, I don't want to anticipate anything. No, I think that what you show it’s a really crystal-clear in in favor of at least a moderate type of fractionation, regardless of the reconstruction and data presented by the Danish Group are really robust and consistent. So, we will see in the close future what would be the indications. I think there will be more recommendations than clear indications, because data exist, not so...not so much in this setting.

Dr Kaidar-Person: Yes, so, I would like to emphasize that I understand why was the fear about using hypofractionation in breasts. Because the early attempt by using hypofractionation in breast were terrible, and patient had severe toxicity from the hypofractionation, but this was done in an era that we didn't understand about dose-homogeneity. We didn't understand recovery time and the planning was terrible. In some cases, it was over 150% of the prescribed dose. So, you can imagine that this what probably caused the toxicity. And again, dose-homogeneity matters. And I love this publication from 2007, Donovan, but it's from John Yarnold's Group. And this study compared the using IMRT for breast compared to the planning, and it's highly quoted in much of the literature, trying to support IMRT for breasts, but when you read the manuscript, you understand that this method was not the IMRT inverse planning R based that we currently speak of. It's actually more like the field-in-field technique, and they use this technique to achieve better homogeneity in case of breast compared to using a 2D technique. And as you can see, dose homogeneity matters and by their technique. So, what they call the IMRT, they managed to reduce significantly the volume that received 100%, 105% of the dose to the breasts and it matters significantly toxicity. And other factors that we need to think about toxicity is the dose-heterogeneity. We have some reports indicating that in case of an expander or the implant, in some cases, it doesn't matter significantly with regards to dose calculations and dose-homogeneity. And for example, the Monte Carlo in some of the reports is pretty reliable for the dose-distribution. And what about boost and bolus? So, to boost or not to boost those patients, some of the

patients are with high-risk for the recurrence. And at least in one of my previous institutions, it was a routine to boost the mastectomy scar with fear of recurrence at the mastectomy scar. Regardless of the stage of the disease and whether the patient had skin involvement. So, we have a nice report, but this is actually not from Alice Ho, it's the same group. I accidentally wrote the incorrect reference. This study was published in the "Red Journal" and they showed that the chest wall boost to the mastectomy scar or chest wall was associated with reconstruction complication regardless of the type of the reconstruction. whether it was in autologous, direct to implant reconstruction, tissue expander to implant, the boost was associated with complication. Additionally, the boost was associated with infections, skin necrosis, and implant exposure. This is a big problem because some of these patients are referred to additional surgeries and often do not have any other alternative. And for implant-based reconstruction, the boost was associated with increased-risks for implant failure. And we're speaking that even rates of more than 20%. So, the addition of the boost that was quite surprising, was not associated with improving of local control, even in high-risk patients. And in this study, the clinical pathological between the boost, no boost groups were without significant differences. So, you cannot say that the boost group had higher high-risk disease. The boosts did not improve local control. So, adding a boost to the scar, unless you have, you know that you have residual disease in an area that the surgeon cannot operate, it's better to take, to operate and not leave residual disease. We do not recommend to boost those patients. And how about the bolus? So, the two discussions here are my...collaborated in a recent paper and are collaborating also in a consensus guidelines that hopefully will be published soon. And we reviewed the use of bolus in the setting of post-mastectomy radiation, in case of chest wall without reconstruction or in case of immediate reconstruction. And according to our report, the bolus just increases toxicity. And in most cases does not contribute to the local control. And we need to remember, it's not that we have a chest wall of a patient and we can bolus it and not take into account the toxicity because some of these patients eventually will need, or will want breast reconstruction. And the result...we might hamper, or this might result in difficulties and more toxicity in performing breast reconstruction. So, I recommend to read this review, and I also hope that our guidelines, consensus guidelines will be published soon. So, I hope you will send some questions in the chat, but I will continue with my presentation and we'll have those questions later. So, radiation in the setting of immediate reconstruction performed badly compared to no radiation at all, but we do have better results in the setting of autologous compared to an implant. And there is a lot of work done from the MROV group from North America. Again, advise breast conserving therapy if you can. Determine the odds for postmastectomy radiation prior to surgery, determining the odds for complication in these patients. We should aim to improve the aesthetic results of the patient, but also the oncologic outcome. And we have recently published a letter commenting that current recommendations for surgeon in choosing the patients who are eligible for breast reconstruction are considerably lacking. They're not really, some of the guidelines are not looking at the oncology indication, but just whether or not the patient is prone for complication and whether or not they consider aesthetic outcomes as a good result. So, you need to act as the clinician and make sure that we choose the patient wisely. Work with the surgeon to understand the surgical procedure. I constantly text, call my surgeons. Where is the boost? Is this clip the area of the tumor bed? Did you put a thread? I read the surgical procedure. I don't understand if you put the retro-pectoral or pre-pectoral, call them, nag them, talk with them. This is how you become a great clinician and a great radiation oncologist. Evaluate the risk of recurrence. Be a detective, look at the imaging. Think if you suspect residual disease, then decide on the volumes at risk fractionation and radiation, and which technique you wanna plan. The fact that you have a VMAT or a tomotherapy, I'm sorry. It doesn't mean that this is the indication that this is the exact technique to treat the breast. Maybe, a field-in-field technique will be much better. Continue with a multidisciplinary effort to improve outcome. We cannot do that alone. I highly, I really depend on my breast expert in imaging, the pathology, the medical oncologist, the surgeons, and my RTTs, physicists, everybody. We work on a team. I cannot, we cannot do this work alone. And we have much more work to do in order to improve the outcome of our patients. We are currently as part of my PhD, we're working on a project with the Netherland National Cancer Registry, and we have a great collaboration with Florence University. The ESTRO guidelines are currently validated in a randomized phase

III trial, and please join. They're looking for partners to join them, take a snapshot of the screen with the number, and you can find it in clinical gov and the contact information. We know that we have several trials that are planned to compare conventional versus hypofractionation in case of immediate reconstruction. And we have very interesting studies looking at primary radiation, then mastectomy, and then autologous-based reconstruction, like the product trial. And we have many other trials that are trying to improve the outcomes of the patients, including Proton Beam based studies in case of breast reconstruction. So, I would like to thank you for listening and thank you to my wonderful colleagues. I have the list, doesn't include all of them, but thank you for the wonderful questions and I hope you have a lot more.

Prof Franco: Thank you, thank you very much Orit for the very comprehensive overview on this like a very interesting and complicated, I would say topic. We don't have any other questions from the audience, but I think we are running out of time, but I have a couple of comments and questions if you're willing to take them. So, you nicely show how the trend of autologous breast reconstruction is decreasing in time while implant-based reconstruction is increasing, even if compared to the literature data, more complications and more failure are described with implant-based reconstruction and also, a less patient's satisfaction, particularly on the long-term with implant-based reconstruction, the satisfaction of patients tend to decrease parallel to the time. But then, if you talk to the surgeon, and the surgeon would mostly say that it is because of the type of reconstruction and with the pre-pectoral implant-based reconstruction, the data and the tolerance with patient irradiated on could be much, much better and potentially this difference in terms of complications failure is mostly due to the fact that the implant-based reconstruction data comprises old data with old approaches and retro-pectoral approaches. So, what's your take on that?

Dr Kaidar-Person: I love this question. So, first of all, I agree with your surgeon that I think with new radiation technique in dose in fractionation, we probably will see better outcomes. The initial experience with the pre-pectoral immediate reconstruction were very poor and it was neglected for a long time because you need to create some sort of pocket to hold the implant. And otherwise, they need to take, to have a lot of residual tissue to create some kind of pocketing only to create a good aesthetic outcome. Now, there are new surgical techniques to do that. Some use ADM, acellular dermis, some use other types of mesh. So, it's not to a biological tissue, and we assume that it doesn't undergo contractor due to the radiation. And if you put it post-pectoral, part of the effect is that the pectoralis muscle undergoes fibrosis and it changes the shape. But I think we do not have a lot of data comparing; in most patients the pectoralis it doesn't look like it looks in anatomy books. It's not that developed. It's usually a very skinny, very thin, and it doesn't cover the whole implant. So, many of the surgeons are already using an additional tissue with an ADM or a mesh to hold the implant. So, I'm not sure if we have enough data to compare, our main concern with pre-pectoral is that the surgeon will tend to leave more residual tissue with the subcutis just to create a thicker pocket to have a more aesthetic look for the breast.

Prof Franco: Thank you, thank you, Orit, it's a good point. I was just wondering, you mentioned that the residual breast glandular tumor is different depending on the time of mastectomy. Your surgeon is a performer and the spatial localization of the recurrence may be different. So, us, as radiation oncologists, in terms of selection and definition of our treatment volumes, or chest volume radiation, do we need to take into account the type of mastectomy? So, meaning do you act differently if you irradiate in a chest wall after modified radical mastectomy, after a simple mastectomy, skin-sparing mastectomy, nipple-sparing mastectomy, is it different, or can we homogenize our approach?

Dr Kaidar-Person: So, we need to homogenize, but in according to the location of the primary tumor, the procedure, I will...we play, sometimes, with the dosimetry just in order to protect the heart, the lung, sometimes you say, oh, I cannot, I do not need to cover all this area. I can reduce a little bit the dose because I have a high cardiac dose. So, it depends. So, I look at the primary where the primary tumor, I understand the procedure and yes, in depending on the surgical type, I sometimes decide that I have an additional high-

risk area that I will like to have full dose, even 98% of the prescribed dose and I... but it's not clinically proven. It's just the logic.

Prof Franco: But the approach could be somehow personalized on the patient.

Dr Kaidar-Person: Yes.

Prof Franco: And the type of procedure that were performed on the patient. Okay, thank you.

Dr Kaidar-Person: Yes, definitely.

Prof Franco: And the last one, I was kind of triggered by the picture you show of the bilateral mastectomy patient with bilateral implant and with the difficulties that you had in planning this patient sparing the contralateral prosthesis. With photos and with VMAT or MRT and field-in-field. Now, I think you touched upon that on your last slide, citing the protons, is it just one, your take on the potential role of proton therapy for post-mastectomy radiotherapy and in reconstructed or unreconstructed breast?

Dr Kaidar-Person: So, it's very interesting. There are few groups that are working on this, including MGH in, from the UK. And I think also the Danish Group is also starting a proton project. I think it might be helpful, if we define the volumes correctly, we might be able to reduce the complications by this, but it's very tricky if we understand where the high-risk volumes.

Prof Franco: All right, thank you, thank you Orit, Icro?

Prof Meattini: I think we are. But just a flash, a flash, a provocative comment on the five-fractions schedule and breast reconstruction, a flash comment and we close.

Dr Kaidar-Person: If I had data, then I would comment but...

Prof Meattini: If you have got thoughts about the five-fractions and the future applications on breast reconstruction.

Dr Kaidar-Person: Of course, I did, because during the COVID we adopted this for many of our patients. And I can tell you that we loved that experience because we've seen, actually, we had the impression that we had less toxicity, even from the 15. We didn't do that though for reconstruction patients. We still use the 15-fraction in case of reconstruction. But for an intact breast, and now the patient, you know, there are rumors we're able to get five-fractions only. So, we have patients coming in asking for the five-fraction magic regimen of breast irradiation. So, I'm looking forward to receive more data about it with reconstruction, it's definitely interesting.

Prof Meattini: Thank you very much, Orit. Thank you for your great presentation.

Dr Kaidar-Person: Thank you for inviting me, it was a pleasure.

Prof Franco: Thank you everyone for watching.