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Do we still need to excise primary focus of breast cancer in patients cCR following neoadjuvant therapy?

Prof Vrancken Peeters: So, welcome everybody. Good evening from Amsterdam. As being said the talk is about: "Do we still have to perform surgery with patients with complete response after primary systemic treatment?" Actually, that's part of the de-escalation in breast cancer treatment that's currently going on. Which was initiated, of course in 1976, by Professor Fisher and Professor Veronesi who started, were the pioneers, on breast conserving surgery. And that was not an easy task. Professor Fisher described that there was a wide spread resistance to this new approach. And Professor Veronesi said it was very difficult for other people to accept this change. But the change happens and long-time breast cancer surgery was driven by tumor burden where in case of larger tumors mastectomy was performed and in case of smaller tumors breast conserving surgery was performed. Nowadays however, tumor burden is only part of what we're looking at and way more we're looking at biology of the tumor and also on the response on systemic treatments. So, what's needed for de-escalation in breast cancer surgery, is a good multidisciplinary approach. So, our MDTs are becoming more and more important to discuss every individual patient. And for example, a patient like this with a T3N2 Her2 positive type of breast cancer. Some years ago, a radical mastectomy was the only thing we started with. And now of course, primary systemic treatment is the first option. Why primary systemic treatments? We know already from previous study from [Audio Not Clear], but also from more recent studies from the nice I-Spy consortium, that when we are able to achieve a pCR. We have a better survival. Of course, when we start with primary systemic treatments, we are able to monitor the response and that enables tailored treatments according to the response. Tailor treatment both systemic as well as locoregional regional. And when we're talking about tailored systemic treatments, we mean escalation whenever it's needed, as being shown by the Create X and Katherine trial. But we are also talking about de-escalation whenever it's possible. And a nice example is that is the current lead going on Dutch TRAIN-3 Trial. In which we try to de-escalate chemotherapy based on the response on the treatments given. And what about de-escalation of local treatments after primary systemic treatments? Do we have to remove the original tumor-bit or can we adapt the local treatment and remove less than that? The first sort of discouraging large study, that was published in the Lancet Oncology, said that we have higher local recurrence rates when we performed breast conserving surgery after systemic treatments. However, as being discussed one year ago in sort of this session as well by my colleague, Dr Gentilini, there are some critical points that you have to take in consideration when looking at this article. Of course, it's based on a large population but an older population. And some of the currently given regimes were not available yet. Furthermore, pre-operative localization techniques were not routinely used and also response-monitoring for example, by MRI was not available. In the current trials, way better results are being shown as being expressed in this chart. And also in this figure of our own study group, in which very nice local results can be

achieved and in inpatients that's started off with large tumors and still underwent breast conserving surgery after primary systemic treatment, because they had a good response. So, in fact, doing less surgery indeed is safe. There two things that you have to take in consideration. You do have to mark the tumor area before you start with systemic treatment and you can either use iodine seeds or another available marker. And response monitoring is necessary. And it's most reliable with MRI. So, here are three patients' examples and all of these patients can have a very good response on MRI. So, there is nothing wrong with performing small surgery on these patients as being shown in the next few slides. Where you see that a gamma probe is being used because in this particular patient an iodine seed was placed before the start of chemotherapy. So, basically small incisions, not only achieving 10 grams and sort of the size of a grape. And of course, you can, it's pretty logical that, in the first patient example, when a pathologic complete response is found, it is safe to perform this breast conserving surgery. In the second patient, with a good response but still some residual disease in the surgical specimen, but radically removed, it's also safe to perform breast conserving surgery. However, in this last patient when there is still residual disease in the show surgical specimen, then breast conserving surgery will not be safe. So ablative surgery, will be necessary in a second surgery. But let's talk about the first situation in patients with a very good or even a complete response on imaging. Of course, the question arises: do we still have to excise the original tumor-bed or is it possible to only, to even omit surgery? That's actually the question, which is becoming more and more important, because since the addition of dual blockade in HER2 positive patients and the addition of carboplatin PARB inhibitors in triple negative patients, very high pCR rates are being achieved. And one reminder it is always possible to send your questions already to the discussants and, we will discuss it at the end of the talk. So, the question was: Can we omit surgery in the patients with the radiologic complete response? The first pioneers in this field were of course Professor Joerg Heil and Professor Henry Kuerer. And they did some pilot studies in a small group of patients, where they performed biopsies and compared that with these surgical specimens. So, relatively high false, negative rates but they were promising, especially when the biopsies were representative. This was enough reason to set up some nice trials from different countries, and the results of those trials were being presented at San Antonio. The trials were the RESPONDER Trial from Germany, our trial the MICRA Trial from the Netherlands and in Australia and the NOSTRA and NRG BROO5 Trial. There were some main differences in trial design. One of them was the type of response monitoring. Two trials used MRI and the other two trials used still ultrasound or mammography as response monitoring. And the other difference was the type of biopsies that varied from 14 gauge to eight-Gauge biopsies. Here you see the design of our MICRA trial in which patients that were treated at primary systemic treatment, all had a marker placed in the tumor beds. On the event primary systemic treatment and in case of a radiologic complete or partial response, they could be included in the MICRA trial. When they wanted that, biopsies were performed and compared with the surgical specimen. We could analyze a full set of 167 patients. 135 of them had a complete response on MRI and 32 of them had a partial response on MRI. This is the division of the different subtypes which is pretty usual. So, in the patients with a complete response, 60% of them also had a pathologic complete response. And even in the patient group that did not reach a complete response on MRI, still one third of them had a pathologic complete response. So, these results immediately show that contrast MRI is very good, but not accurate enough to detect pCR or to fully detect residual disease after primary systemic treatments. So, when looking at the results of the patients with a complete response on MRI, there was a little bit disappointment with the very high false negative rates. The false negative rates of biopsies compared to the surgical specimen in the patients with the partial response on MRI, was a little bit better. But still, actually, the conclusion of this trial was that performing 14-gauge biopsies in patients with a very good response on MRI, is not accurate enough to really detect a patient with a pCR. So, therefore based on these results it's too early to omit breast surgery after primary systemic treatments, since residual disease is missed in about 2/3 of the patients. The other trials basically had the same results as being shown this slide. So overall, it is too early to omit surgery. And mainly because there are some consequences of missing residual disease. Of course, pCR was always used as prognostic factor but more over at currently, it's being the amount of residual tumor is being an indication to adjuvant treatments, as being shown by the Create X and the Katherine trial. And one also has to have to

realize that of course, all these patients will undergo radiation treatments. And in case a recurrence does occurred, that immediately means that mastectomy has to be performed. So, quite some consequences. So, from this perspective we really need to do some more research and find out if we can have a better response prediction-model, in the future. And what about the axillary treatments after primary systemic treatment? Because, of course, not only breast pCRs occur but also axillary pCRs. And also, those rates are increasing, especially in patients that do have a breasts pCR, very high pCR rates in the axillary are being achieved. How do we find these patients? We all know that whatever noninvasive manner you use, they are not accurate enough to restage the axillary after primary systemic treatment. And there are a lot of very nice trials that investigated the role of sentinel nodes in this situation. And most of those trials showed that the identification rate of the sentinel node is way lower, compared to the sentinel procedure in the primary surgery setting. And moreover, the false negative rate of the sentinel node procedure is way higher. And only a acceptable false negative rate of less than 10% can be achieved, when two or three sentinel nodes can be found. And then the largest study the SENTINAL trial, they investigated in how many patients that was possible. In the SENTINAL trial they had a false negative net rate of less than 10%, when three or more sentinel nodes could be achieved. And as you can see here, that was only possible in 25% of the patients. I'm sorry, that was only possible in a 34% of the patients. I made a miscalculation. But still, that means in 2/3 of the patient that was not possible and that on top of the lower identification rates. So, one was looking for alternatives and for example, the TAD procedure and we introduced the MARI procedure. The MARI procedure is based on marking one of the involved nodes prior to systemic treatments. In our case with an iodine seed and look at the response of these nodes. And that response was representative for all the other nodes. The MARI procedure has shown to have a identification rate of 97% and a false negative rate of 7%, which was 4% when isolated tumor cells were excluded. In the meanwhile, we did the next step to see if we could really do tailored axillary treatments by combining optimal pre-operative or of pre-chemo axillary staging by PETs. Plus, post-op axillary staging by the MARI procedure. And that led to the following schedule. So, patients were divided into groups having either up to three pathologic lymph nodes or more than that. And then, dependent on the pCR or no pCR in the MARI node, the axillary treatment was adapted. So, this patient group did not undergo axillary treatment. Here axillary radiation was most given and only in this group of patients, they still underwent an axillary clearance in combination with radiation. This procedure is possible, this protocol is possible and then you're interested in the results, the longer-term follow-up results are gonna be presented at the EBCC meeting which is in the beginning of October. And this having said, I would like to thank you. I don't know who it is exactly, but on the other side of my screen, for your attention and of course I would like to thank our whole team back in Amsterdam for all the work that has been performed, to have the results of some of the studies that I presented. Dr Wysocki: Thank you very much for your talk. You are mainly talking about de-escalation of surgery and, do you think is it any limit of the de-escalation? Your conclusion was there's still no place to omit the surgery after pre-operative chemotherapy, systemic therapy in the breast by doing a biopsy. But I think that's the direction we are going to. So, do you think is there any limit for the de-escalation of surgery in the future? There will be any place left for surgery in the breast axilla?

Prof Vrancken Peeters: Yeah, I think that's in the future breast surgery will still exist but will be mainly reserved for residual diseases or bulky diseases. And I really think that we will find a way to better predict the patients with a pCR. And of course, what we still don't know is, except from the facts that now we also wanna tailor these systemic treatments in case of residual disease is still found. But what we don't know is how important is, let's say, leaving a little bit of residual disease behind. I think we can all feel that, let's say, when we leave behind isolated tumor cells we still have to radiation. But it shouldn't sort of ... The load should not be too high, but what is too high? That's a difficult question. But I think that's we will go on with de-escalation. Our current approach didn't work, yes. And you were looking closely to the results of the other studies, a combination of the results which might, of the techniques, might already be better. Because I think we had a nice response monitoring by MRI, not all the other studies did. On the other hand, we had way

smaller biopsies. So, maybe even some larger biopsies and accurate response-monitoring will move on and we will get there some time, yeah.

Dr Wysocki: And well, we are talking about the response monitoring by imaging. You have said that MRI contrast hence MRI is not good enough to predict adequately the response. But, are there other imaging modalities which might be useful in that circumstances. That is a question from the audience I'm referring to it. What is the role of tomosynthesis to assess the residual disease? Can you comment on that?

Prof Vrancken Peeters: Yeah, it's a very important question I think and... Well, actually in Amsterdam we're very lucky that we are able to perform all these MRIs. And I realized that it's definitely not possible to do that in a lot of other countries. And other imaging modalities are being tested as well of course, easiest ultrasound in combination with the mammogram. The ??others?? and the PET-scan for example. I do not know if the tomosynthesis is being tested in this situation. But it's...

Dr Wysocki: As far as I know—

Prof Vrancken Peeters: I do know that PET CT doesn't perform better in response monitoring than the MRI, that's for sure. And MRI is better again than the normal mammography and ultrasound. And the thing is of course you can see a nice response, but are you able to really identify this patient that has a pCR? That's not possible yet. But with none of them imaging modalities.

Dr Wysocki: I think you have shown it very nicely, but there was a huge discrepancy between radiological complete response and pathological complete response in your studies. So, with proves that even MRI, which as far as I know is by far better than tomosynthesis in assessing villus pores cannot be used for that purpose. What wonders me also you said that in showing that we cannot omit surgery you said that a vacuum biopsy is not good enough to, as by now. You said that in case a recurrence will be seen, the only option is mastectomy. So, I think why you said that? Because I think still if after neoadjuvant chemotherapy and we will omit the surgery based on the negative result of biopsy in case a recurrence would be seen, why mastectomy is always, is the only choice?

Prof Vrancken Peeters: Well, let's say that the way these trials were set-up, was omission of surgery. But radiation treatment was then always indicated. So, then in the patient that has been radiated already. Second breast conserving surgery, well, but that would be another sort of era, another option. There are multiple ways to go so. There will also be a patient group of course, the patient group for example, with no nodal involvement but only breast involvement. Where you can even think of not performing the radiation. And then it's sort of more comparable with a real wait- and-see approach and then you can have all the treatment options still available. Yeah so, it's difficult the way the field will go. But what you don't want is perform radiation treatment of the breast and then have a recurrence as well. The current standard of course, then is in a patient that had breast conservation with radiation treatment is mastectomy. But maybe we should think differently in this new era. But that's still to be discussed

Dr Wysocki: I would like to come back again to you also mentioned in your reply right now, the node positive patients. I think it needs to be underlined, I don't know how would you comment on whether that positive nodes need to be marked with a marker as well. Not only the primary tumor in the breast. Can you comment, because it's not widely accepted as far as I can see. And I think it's very important if we are really willing to de-escalate the surgery.

Prof Vrancken Peeters: Yeah, it's nice that you mentioned that still of course, this whole, well, the first step was treat patients with primary systemic treatment whenever they need systemic treatment. And I think that's something that more and more breast cancer groups do. Then of course, the next step was to adept especially the breast surgery to the response. And the axilla was a little bit forgotten in a way that, breast conservation was performed but still axillary clearances are performed in every patient. And now, there was

a lot of debates on how to adequately stage the axilla. And I think there's not one best option yet, but you do have to realize that you can stage the axilla after primary system treatment. The way I showed it's just only a marker and, in our case, directly and iodine seeds, which is the MARI procedure. But of course, there are also other options in which the MARI type procedure of MARI like procedure is combined with the sentinel nodes. In some clinics they mark one of the nodes and then put a wire in it. In some other clinics they mark one of the nodes and then give some extra technetium in there. So, there are a lot of different ways. But I agree with you that, try to find one of those options and apply that in your clinic. So, to spare at least some of the axillas. So yeah, when you don't have that routine in your protocol yet and you do have primary systemic treatments in your protocol already with marking the breast, then also mark the axillary node; RAD have one of them. To see if de-escalation is possible there as well.

Dr Wysocki: Absolutely right, I'm happy that you underlined RAD because, even complete pathological response in the breast primary does not translate itself into complete pathological response with positive primary positive lymph nodes. And we need to remember that. Okay I think, we can finish now. I really would like you to thank for your effort and for your very clear and informative lecture. And I would like to thank the European School of Oncology and to the attendees and to you as well. Thank you very much and goodbye.

Prof Vrancken Peeters: Yeah, thank you as well and hope to see you sometime in my life somewhere.

Dr Wysocki: Thank you and bye-bye, thank you.

Prof Vrancken Peeters: Okay, bye-bye.

Dr Wysocki: Thank you.