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Management of surgical margins

Dr Meani: Good evening, everybody. Good evening, Christoph. Thank you for accepting the invitation to assist me tonight. Thank you, everybody, for joining us tonight. It's a real pleasure to me to be here and participate to this e-ESO BRESO pathway that I have the pleasure to coordinate being one of the co-founders of the BRESO, Breast Surgical Oncology Certification project and, of course, being a long-time collaborator for e-ESO, European School of Oncology. Tonight, we will discuss the much debated and always current topic of how to define and manage inadequate surgical margins. And please, remember that you will be able to send questions or comments anytime throughout the whole presentation by clicking on the Q&A button of your screen. Let me start introducing the topic by giving you a definition and some fundamental consideration on current evidence. Margin status is defined as the presence or absence of malignant tumour cell on the edge or close to the edge of a surgical specimen, not just lumpectomy but also mastectomies, of course. The presence of disease on or close to the margin is considered as a surrogate marker of residual disease in the breast, and thus is related with a higher risk of recurrence. In particular, it impacts on the patient's risk in breast tumour recurrence. As a matter of fact, for a long time, there has been a great debate on what an adequate margin was and there is great variation in margin definition, or there has been great variation, and there is variability not only in the definition but also in the rates of positive margins and, consequently, in the re-excision lumpectomy rates. Historically, the involvement of a resection margin was considered likely the most important prognostic factor for recurrence and telling an indication for re-excision and thus, causing an important burden on the patients and also on healthcare systems across the globe. But in order to try to understand what the proper management of surgical margins should be in clinical practise today; I suggest to start from three apparently simple questions. Number one, what's the aim of breast conservative surgery in your opinion? Is it to remove the whole tumour in the breast of the patients with an early breast cancer? Or much differently, is it to remove the index lesion with a surrounding safety margin such as the residual tumour, which is probably there? Is the burden low enough to be further controlled by adjuvant treatments while preserving cosmetics to its best? Question number two, what should be considered adequate today in terms of surgical margins? And number three, in this era of multidisciplinary approach and treatment to breast cancer, what's the real role today of surgical margin in the control of the disease? In other words, does it still matter what the margin is? Well, to try and answer the second and the third of these questions, Nehmat Houssami published this quite old work in 2010, which was a landmark study at that time. It was a meta-analysis on about 21 studies and more than 14.000 patients. And in this work, she looked at the role of margins under two different scenarios. The first one, in the first scenario, she compared negative margins with those patients with close or positive margins. And in the second, on the right-hand side of this slide, she differentiated three different thresholds of margins with one millimetre, two millimetres, five millimetres. And she was able to find a highly significant difference in terms of local recurrence when comparing patients who had negative clear margins to those who had close or positive margins. But she was not able to find a significant difference when comparing different thresholds. She found a trend but was not statistically

significant, in particular when adjuvant treatment, radiotherapy, or monotherapy were given. So, she could conclude that negative margin did have to be pursued while she was not able to define a clear threshold of thickness to be sought after. A couple of years later, Nehmat Houssami was one of the authors of these guidelines issued in 2014. At that time, a multidisciplinary consensus panel was convened with the purpose of examining the relationship between margin-width and in-breast tumour recurrence rates and draw a guideline intended to help physicians and assist them in the clinical decision-making and in the discussions with their patients. And in this meta-analysis, the presence of ink on tumour cells was found to be associated with at least a two-fold increase in breast tumour recurrence. So, involved margins, two-fold increase in local recurrence. And this increase was not nullified whenever a radiation therapy boost was given, was modified by systemic treatment, or by favourable biology. So, the authors concluded that the definition of adequate margin for invasive breast cancer should have been no ink on tumour, and there was no evidence that any bigger margin was giving any better result. With the only exception, though, for breast conservative surgery performed after neoadjuvant systemic treatment. At that time, in that particular situation, they suggested a two-millimetre margin width. So, it's not surprising that at the following St. Gallen consensus conference in 2015, the panel of the experts when was asked about minimal acceptable margin width, voted to the great majority, 92%, in favour of the no-ink on tumour threshold. And what was maybe more interesting is that, at that time, when they were asked in particular about DCIS in-situ disease, they also agreed at that time that there should be no difference. And even for DCIS, no tumour on ink was, according to them, the reference for margin width. Now let me open a small digression about this topic. Why should this, or could this be a surprise? Is there any reason, in other words, to suggest larger margins in DCIS? Well, we know that historically there has been an even larger lack of consensus among surgeons about the optimal margins for DCIS. And probably the reason is that the growth pattern of DCIS is often a discontinuous pattern within the glandular ducts. So, there are often gaps between tumour deposits. And this is probably why larger margins even up to one centimetre had historically been suggested by many authors. But a consequence of this was an even higher rate of re-excision whenever DCIS was involved. And these two studies are an example of the great confusion that was there upon DCIS. The first study published in 2009 by Dunne and Morrow, for example, it was done on about 2.500 patients, showed that having involved margin was definitely worse than having one-millimetre margin clearance. And that having one-millimetre of clear margin was worse than having a two-millimetre margin. But they found no further gain achieved in the group of patients that had five or more millimetres of clear margins. On the other side of this slide, we have a second work published a few years later by Dr Wang that found on the contrary that patients with 10 millimetres margins seem to have a much better outcome than those with two millimetres margin. So, in other words, surgeons, with cosmetic constraint, should have achieved negative margins as wide as possible at their first attempt when treating DCIS patients. So, in a nutshell, the degree of confusion regarding DCIS was even higher and difficult to manage than with invasive disease. Please remember, you can ask questions or send comments, and Dr Tausch will be there to help you with this. For this reason, a couple of years later, in 2016, the experts were induced to get together again and draw a second guideline specifically for ductal carcinoma in-situ. And with this meta-analysis on almost 8.000 patients, ink on tumour was found to be associated with at least two-fold increase, again, in breast tumour recurrence. And this in case was not nullified by giving whole breast radiation treatment. While two or more millimetres margins showed a significant reduction in breast tumour recurrence. And also, the authors showed that there was no difference for any bigger margin to be sought after. So, since the publication of this work, these guidelines, in 2016, the new definition of adequate margins for in-situ disease was two or more millimetres, and thus, since 2016, we have two different thresholds differentiating safety margins in invasive disease, no-tumour on ink, and in-situ disease, two or more millimetres. What was also significant and very interesting about this publication is what the authors concluded, though, when referring to the grey zone of clear but close margins. Those cases in which we do achieve clear margins must be smaller than two millimetres. And in this case, they suggested that clinical judgement should be used in determining the need for further surgery in patients with those negative margins narrower than two millimetres, meaning that other factors should have been taken into account

whenever deciding for re-excision. Other factors like age, biology of the tumour, grading, extension of the close margins, pattern of growth, and so on. So, with no surprise, at the following St. Gallen conference in 2017, the majority of experts seem to have changed their mind according to the new guidelines and abiding to them. Nevertheless, this time, the consensus was not so unanimous, 62 roughly percent against 34. So, in this case, there was a narrower majority in favour of the new margin threshold of two millimetres. So, does that mean that confusion is still in place? For the sake of complete wellness, let me tell you what happened in the next edition of the St. Gallen conference. In 2019, the experts went again over the topic of margins and they stated that no-tumour on ink had to remain the standard for invasive breast cancer, this time, even after neoadjuvant systemic treatment. So, this time they suggested against the recommendation they published beforehand in 2014 in this regard. And another interesting statement was that in case of focally positive margins, even if re-excision was definitely the preferred option, a boost of the primary tumour bed may also have been an acceptable option. So, this shows a general intent to reduce as much as possible the re-excision rate as a general rule. In 2021, it was the time for suggesting the use of the boost on tumour bed in case of that grey zone of clear closed margin in DCIS resections. And finally, just a few days ago, Christoph and I were there, even if margins were not one of the main topics of the last conference, it was reiterated that no-tumour on ink is to be considered adequate in breast conservative surgery even after neoadjuvant chemotherapy. And this indication has been reinforced by the data published by the group of the Memorial Sloan Kettering just two years ago. Any question coming up? So, after all this chit-chatting on the millimetres debate, I would like you to think about it and to ask yourself, should we really place such a great emphasis on achieving specific negative margin width? In my opinion, there are so many different technical limitations that causes substantial variability in margin assessment such as those related to the specimen characteristics, those related to the technique that's employed by the pathologist for the specimen examination, and all the problems of communication between the OR, the radiologist department, the pathologist. Let me briefly show you what I mean. First of all, the surgical specimen. We must keep in mind that the specimen is soft. It's malleable. It's shiftable. The surface may be incised while during resection and get coagulated. Specimen may flatten ex-vivo. The ink on surface may track into those incisions and into the specimen making it difficult for the pathologist to determine the true resection margin location. So, all these factors may reduce the reliability of margin assessment. And then, secondly, the technique for margin assessment is not standardised. We have, for example, a shaving method, and a slicing method. And it has been demonstrated by several publications that the rate of margin involvement is largely dependent on the method that has been applied and we have to keep this in mind also. And finally, the aspect of communication that cannot be overlooked. Remember, surgical specimen is oriented by the surgeon intraoperatively and this procedure usually is not standardised and that can cause misunderstanding. So, remember, your report for the pathologist is very important. You should document clearly how the specimen was oriented, if the fatty fascia was removed from the muscle for example. And then, if you are applying and if you're routinary using the radiography, the X-ray of the surgical specimen, a communication with the radiologist is also of utmost importance. So, you can understand overall that this complex network of communication is not flawless in real life. So, we can conclude that the final pathology, even if it gives us a seemingly precise information about margins, in reality, is not absolute truth. On the contrary, in my opinion, we should understand that it probably offers no more than general indication on the likelihood of having residual disease in the breast and possibly its extent. So, it should be interpreted with a grain of salt whenever deciding on re-excision for our patients. And what's the real dimension of the problem out there, in clinical practise? I can show you results from very old studies, but just to give you an idea on how variable it used to be the rate of margin positivity involvement. So, in these figures, we range from roughly 15 to 50%. It's enormous. And if you want to look at more recent studies, we can get an example from this American study published in 2017 by Monica Morrow, described the trend in the USA that dropped significantly from about 35% of positive margins to roughly 20% between 2013 and 2015. Those years when the guidelines on invasive breast tumour were disseminated. And this was particularly true for larger centres with high caseloads and experienced surgeons. And if you prefer to look, oversee in our old continent, this is a study from UK also published in 2017. And

the average national re-excision rate in those years in UK, according to this study, was around 17%, the majority of re-excision done for tumour at the inked margin and not for closeness. And on the other end, if you want to look at what the benchmark, the current quality benchmark might be for re-excision rate, we can look at the EUSOMA guidelines, for examples. And here, it states that the proportion of patients, in case of invasive cancer, receiving a single breast operation for primary tumour should be 90%. In other words, 10% of re-resection for margin inadequateness. And when talking about DCIS, the same numbers are given, even in this case, they accept up to 30%. Reiterating the fact that DCIS is a bad company to deal with. Again, please ask questions or send comments if you like. What can the surgeon do to improve these results, to reduce the rate of margin inadequateness? Are there any options for our surgeons? Yes, there are. And, for example, in this paper published by Landercasper, I think, in 2015, there are many things that can be done and they can add upon each other, even if there isn't, unfortunately, as we all know, there is no one single solution to the problem. But let's take a look at some of them. Formal preoperative planning of surgery is very important, and surgery should be preoperatively discussed in an MDM, in a multidisciplinary team meeting where individual risk factors should be considered on a case-by-case fashion. We can increase the surgeon's caseload by concentration of cases. The higher the caseload, the higher the experience of the surgeon, the lower was the involvement rate of margin. We can use, and we should use adequate state-of-the-art preoperative imaging. We should resort to oncoplastic techniques whenever indicated to increase the volume of our excisions without compromising the aesthetic outcomes. We must, or we should use image-guided localization techniques, for example, intraoperative ultrasound, in particular for non-palpable lesions. And also, we can use intraoperative X-ray of the specimen. And finally, if any is available, we might use or apply specialised new techniques for intraoperative margin management. So, some of these listed points are quite obvious. While I would like to consider with you some of them, and I would start with the old-fashion of intraoperative margin frozen section. Frozen section on margin has historically been suggested as an intraoperative modality for margin assessment. And according to old studies, it seems to be able to reduce significantly the incidence of positive resection margins. But in reality, probably this effect was highly dependent on the baseline rate of the excision. And in well-performing centres, the contribute of this procedure, frozen section, in reducing positive margin is likely negligible. Any significant advantage has never been demonstrated in this setting. And so, as a take-home message, I would say that frozen section on margin, except some particular situations, should not be used on routinary basis. Secondly, I'd like to spend a few words on specimen X-ray. First of all, we must understand and remember that the primary role for specimen imaging is to document the removal of non-palpable lesions and their markers. That's the point. In fact, there's low-level evidence that supports specimen radiography as a method to assess the distance, reliably, of the lesion to the margins and therefore, to potentially reduce re-operation rate. Nevertheless, in many centres, my institution included, it is current practise to perform specimen X-ray. But remember, in this case, it's very important that both the surgeon and the radiologist look at the specimen and communicate with each other in the correct fashion. Third, I would like to mention the use of intraoperative ultrasound, which, in my opinion, is a very useful technique. And it's not a surprise that intraoperative ultrasound is largely used in Switzerland because here breast surgery is often, not only, but often performed by gynaecologists who get largely exposed to the use of ultrasound during their clinical training and so, they are very accustomed to the use of ultrasound probe and they like to bring it to the OR. Finally, special techniques, if any exists that can really help. This is a historical slide. I would like to show you this because many different possible approaches based on different new technologies have been proposed and evaluated in the seek for a solution to a topic that has never been resolved. In this case, the MarginProbe system was a technology based on the management of transmembrane electrical potential, which seemed to be promising, but, unfortunately, did not meet the expectations showing too many false positive results. More recently, a different technique is the proposed application of the use of confocal microscopy. These two are two different devices, two different examples of devices specifically designed to be used in the OR for real-time evaluation of surgical specimen. They're supposed to reveal microscopic tissue morphology and aid in intraoperative evaluation of surgical margin asking the surgeon to become a little bit of a pathologist and

develop those skills. Maybe Christoph Tausch can tell us something about this later on. But for the time being, to my knowledge, no final conclusion can be drawn on the use of this technology. And then, let me spend a few words on MRI. This is not a special technique, obviously, and the question is not whether a preoperative MRI can efficiently improve breast conservative surgery outcome because this has been already addressed. We can see in this slide, two different studies that you probably all know. The COMICE and the MONET trial that demonstrated that MRI should not be used routinely for preoperative workup of breast cancer patients to reduce re-operation rate. But here, I'm referring to a different use of MRI, the use of supine MRI, that can actually replicate the surgical position of the patient and hence, it carries the potential to increase the precision of breast conservative surgery in terms of localization in particular for non-palpable lesions and maybe decrease the re-excision rates for inadequate surgical margins. Let me show you two examples, two studies that are currently ongoing overseas in US. Both based on the application of supine MRI. The one on your left-hand side propose the use of MRI as a navigation tool, a navigation method, while the other is more peculiar, let me say, and proposes the use of a patient-specific 3D-printed form based on supine MRI-derived images to be used as a template to place in the surgery room, on the breast of the patient to guide tumour localization and tumour resection. Both of them are under investigation and are quite cumbersome studies, but who knows. We will see. Now, it's time to go back to reality and to present time and it's probably time to wind up with my presentation, but I would like to stress a concept I am convinced about. In other words, in my opinion, the best results for the moment being can be obtained by a multidisciplinary evaluation together with the multimodal approach to surgical resection, in particular for breast conservative surgery based on interdisciplinary discussion and on routinary use of intraoperative ultrasound and specimen X-ray. And let me show you with one single slide what I mean. For every operation, I like to sit with the radiologist and discuss, analyse together every single case. We always use or apply ultrasound visible devices, clips, and wires to guide our resection. We carry the ultrasound in the operating room and whenever needed, we can apply oncoplastic techniques for larger resections. Finally, we do take an X-ray of the surgical specimen. By this multimodal approach to breast resections, we have been able to significantly reduce the rate of our re-excisions as demonstrated by this internal analysis we did back in 2020. And we noticed a sheer drop from 2011 when we finally introduced these methods bringing our numbers down below the famous threshold or benchmark of 10% and plateauing around 7 to 5%. So, in summary, what's the take-home message? What are we supposed to do to manage positive or close margins today? Let me make a distinction. If we simply want to apply international guidelines, it's simple. In case of lumpectomy for invasive cancer, with or without DCIS component, with negative margins, meaning with that no-tumour on ink, including the scenario of post-neoadjuvant chemotherapy, no re-excision is recommended. In case of a lumpectomy for an in-situ cancer with negative margins, and with this I mean equal or more than two millimetres, no further surgery is recommended either. In case for a lumpectomy for in-situ cancer, with the grey zone of negative but close margins, below two millimetres, guidelines state that re-excision is recommended, but additional risk factors should be considered before actually bringing the patient to the OR. And finally, in case of lumpectomy with an involved margin, either by invasive or in-situ cancer, re-excision must be performed. Any reason for not performing should be documented. But I believe that our aim should be something more sophisticated and I think that we should aim at critically analysing the problem. And in this case, we should consider several things. First of all, the positive margins we know that significantly increase the risk in-breast tumour recurrence. And we also know, as we said at the beginning of this presentation, that not all cancer is removed even when we achieve negative margins. As the aim of breast conservative surgery is to remove the index lesion with a surrounding safety margin and nothing more. It has become evident through the years that the width of negative margins must be considered only one of the many factors that govern local recurrence, and probably, that the obsession with small one to two millimetres differences, it does not make that much sense. Rather our aim should be to identify that subset of patients which likely have a large residual tumour burden after surgical resection after conservative surgery. I believe that the adequateness of close margins should be considered in a case-by-case fashion in the context of many, multiple clinical factors, unifocality, multifocality, biology, age, and also consequences of re-excision. Think of new hospitalisation, think of new

anaesthesia, surgical procedure, likely worse cosmetic outcome, likely increased healthcare costs. So, as a final remark, I would say that in the era of excellent adjuvant treatments there are very few circumstances that should induce re-excision for clear but close margins and that the decision should always be made multidisciplinary. And even in presence of a focal tiny involvement of the margin, the consequence should not always be straightforward to the OR. And having said that, I thank you very much for your attendance, for your attention, and I'm ready to take questions.

Prof Tausch: Thank you, Francesco, for this excellent presentation and it was a great overview, overall, topics in this very crucial topic. And there are some questions, and I want to start with the question from the audience. Is local recurrence risk depending to the intrinsic subtype of the tumour?

Dr Meani: As I said, yes. As I said, it's not just the presence of tumour on the margin but many other factors. And one of those factors is definitely the aggressiveness. So, in other words, the biology of the tumour. So, yes.

Prof Tausch: Okay. And then, the other question is, if there are positive margins, is it influencing local relapse or do we have also an impact on survival outcome?

Dr Meani: On severe outcome, you said?

Prof Tausch: Survival.

Dr Meani: Survival.

Prof Tausch: Yeah.

Dr Meani: Well, I would turn the question the other way around. Does local recurrence impact on survival?

Prof Tausch: Yeah.

Dr Meani: It depends. I mean, definitely, it can for DCIS. As we know, 50% of recurrences in DCIS come back as invasive tumour. And if you shift from a non-life-threatening disease to a potentially life-threatening disease, yes, it can. On the other hand, we know that from very old-time studies that are the basis of conservative surgery of the breast, we also know that even if with conservative surgery we do increase a little bit the risk of in breast recurrence. This does not impact on a general basis on final overall survival.

Prof Tausch: Okay.

Dr Meani: What do you think, Christoph?

Prof Tausch: There's little impact on...

Dr Meani: Little impact.

Prof Tausch: On survival outcome. Yeah, but it depends also on other factors. Yeah. If there's only a local recurrence without another recurrence, a distant recurrence, I don't think that there's any influence on the survival. And then, there was also a question, if there are positive margins and you do further radiotherapy, is boost indicated in these patients for all of them or only in selected?

Dr Meani: As I said, it can be indicated in selected cases.

Prof Tausch: Which cases are these?

Dr Meani: Yeah, as I said, I mean, for example, the guidelines from the St. Gallen conference suggest that a boost can be given for focal involvement of the disease or for in-situ disease with close but clear margin. So, that grey zone below two millimetres. So, these are cases when a tumour boost can be discussed instead of a re-operation.

Prof Tausch: And would you also advise that the pathologists should always state if there is a close margin or if there's positive margin to which extent is this?

Dr Meani: Absolutely, yes. Because extension of positivity and pattern of growth is also very important. There are situations, in particular for in-situ disease within a lumpectomy specimen you find scattered DCIS, here and there, all over the specimen. And maybe, you have clear margins all around, but are you sure that in that situation there is no significant residual burden in the breast? So, what things should be evaluated? The extent of the involvement, the extent of closeness to the margin, but also the pattern of growth within the surgical specimen.

Prof Tausch: And then, there is another question that I would also like to discuss with you. Is there a difference for DCIS, for pure DCIS or the extended DCIS or added DCIS to an invasive tumour?

Dr Meani: So, the answer is, yes, there is difference. Guidelines warn about resect positive or close margins whenever a pure DCIS is close to the margin or at least consider resection, while guidelines state that whenever it's a mixture of invasive and in-situ, the in-situ component, even if extensive in-situ component, can be neglected. If you ask me why, I have to admit, I have no the answer.

Prof Tausch: It would have been the next question. Do you know?

Dr Meani: I don't. I tried to ask a pathologist recently, but I didn't get an answer.

Prof Tausch: That's interesting. So, thank you. For me, it's a very important statement of you, it was the multidisciplinary collaboration, the close lab collaboration with the radiologist and the pathologist in this situation. And always, if there is one focal involved margin, then it is also to discuss in the multidisciplinary tumour board, depending on other factors, depending on the age of the patient, what other therapies are intended, and so on. I think that's the most important statement of you that I want to emphasise.

Dr Meani: Thank you. Yeah.

prof Tausch: So, I don't see any more questions from the audience. I think that we are also finished with the time for us and I want to thank you for this excellent presentation.

Dr Meani: Thank you very much. Thank you very much for your assistance, and it was a real pleasure for me. Thank you.