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Primary axillary surgery: techniques and indications

Prof Karakatsanis: Good evening from me and thank you very much for the invitation. Today, we will be discussing the topic of axillary mapping in the upfront setting. So, I will just start by sharing my screen. So, welcome to this European School of Oncology webinar. We will be discussing primary axillary surgery with techniques and indications, and I will be actually focusing almost exclusively to the concept of sentinel lymph node biopsy since it is what is currently dominating practise, and we will be discussing axillary dissection as an extrapolation to that. From my part, these are my disclosures and please, remember that you can ask questions and send comments at any time so that we can discuss afterwards. So, the sentinel lymph node is the first lymph node in line to the regional nodal basin and it was a concept that was introduced in clinical practise in the 90s through the drug trials and initially through melanoma and then, in breast. Despite the fact that it is a much older story since the first attempts to discuss mapping the first node of the nodal basin were already presented and discussed and researched upon on the 70s with penile cancer. It is considered to be representative of the nodal status with very false negatives, and it can give us an accurate idea of the nodal spread in breast cancer. The discussion about sentinel lymph node biopsy has been an evolving land and timescape, so to say, because we started from early on with standard axillary lymph node dissection, because it was back then believed to be of therapeutic value, and slowly on, the technique was adapted until the new millennium, in 2000, where it became routine for the negative axilla. And then, we pushed the boundaries a little bit more with discussing whether it was enough treatment in patients with low-volume axillary disease as found on specimen pathology, and further on, in the setting of neoadjuvant treatment. However, today, we will not be discussing neoadjuvant treatment, and we will stick to the upfront setting as we say. So, sentinel lymph node biopsy in current practise is actually something that has to do with the majority of our patients in the sense that if we look at these World Health Organisation data, 61% of patients do have only localised breast cancer without any evidence of nodal spread upfront, but also on post-operative pathology. But there is also 31% that will have some regional spread and that will probably not be high volume enough to motivate further surgery. Moreover, the ever-growing implementation of neoadjuvant chemotherapy and primary systemic therapy suggests now that patients with limited disease that will respond satisfactorily to therapy, may actually avoid axillary clearance. So, more or less, we are talking about a practise that is the clinical reality for 90% of our patients. If we discuss what the relevant questions are, the first one is indication. So, do we need to do it, and when do we need to do it? And then, the technical part, how would you do sentinel lymph node biopsy? So, we will just stratify what we have depending on evidence, and we will start by focusing ourselves on the routine use of sentinel lymph node dissection as supported by level 1a evidence, which means RCTs. So, in the scenario of a clinically node-negative axilla that undergoes sentinel lymph node dissection and proves to be pathologically node-negative, there is an increasing bulk of available evidence from many randomised controlled trials that suggested that this procedure came with a very high detection rate and low false negatives. And the oncological outcomes suggested that the overall survival, the disease-free survival and the axillary recurrence rates, were

completely comparable to the ones that we had with axillary node dissection. These results were moreover comparable regardless of the type of breast procedures that had been performed, and at the same time, we saw that sentinel lymph node dissection came with less morbidity and better quality of life. With regards to the false negative rate, we know from the NSABP-B32 that it was dependent on the number of lymph nodes retrieved with one node suggesting a false negative rate of about 20%. But reassuringly, this number dropped down to less than 7% with the harvesting of more than three nodes. Currently, we know that three nodes or more yield very low false negative rates, around 5%, but increasing the nodal yield suggests that we may be increasing morbidity, but post-five, we do not significantly reduce the false negative rate of the procedure. Moving further to the next step, that is, the clinically negative axilla which proves to be positive on pathology with micro or two macro-metastases. There is a constellation of well-conducted randomised controlled trials that, despite the differences in methodology and inclusion criteria, suggest the same results. Meaning that we have comparable overall survival, disease-free survival and axillary recurrences. We will be discussing with Professor Tinterri and Professor Gentile afterwards about that a little bit more. But the interesting thing is that these results were completely comparable despite the fact that the inclusion criteria had T1 and T2 primaries, but with different size cut-offs. Inclusion or not of multifocal cancers, as we know from the AMAROS trial, and all these trials had a subgroup of patients that had undergone mastectomy with the exception of the ACOSOG Z0011 trial. All trials suggested that we had less morbidity, we had better quality of life, and at the same time, differences in how patients were recruited such as, for example, the non-uniformity in performing standard axillary AUS at baseline. And the biologic low event rate leading to a low recruitment of active population and the radiotherapy protocols have been discussed. However, differences in trials and long-term results suggest that there is no difference. So, from that, we can already summarise that in the context of randomised controlled trials, we know that sentinel lymph node dissection is adequate and safe and accurate axillary staging for all patients that have a clinically negative axilla where the specimen pathology from the axilla suggests that there are none or up to two macro-metastases. Moving further, in the absence of level 1a evidence, so there are no randomised controlled trials, the first category that comes to mind is upfront surgery for larger tumour. So, T3 tumours, meaning tumours that are more than 5 cm but do not engage the skin, do not engage the chest wall, and are not inflammatory breast cancers. This available evidence stems from cohort studies and the existing evidence suggests a low pooled false negative rate of approximately 3.1% and a very high detection rate. However, the available evidence suggests that the prevalence of metastasis in patients with T3 tumours was much higher. In current practise, however, this is something that we do not usually do because, on the one hand, most countries have screening programmes that suggests that most tumours will be detected in an earlier stage, on the one hand, and on the other hand, as we discussed previously, the implementation of primary systemic therapy suggests that this axilla will probably be explored surgically after the completion of neoadjuvant chemotherapy. In the setting of locally advanced breast cancer or inflammatory breast cancer, there is scarce available evidence and the mechanism around that is that the notion of lymphatic spread of cancer emboli, in the intracutaneous and subcutaneous lymphatics, will affect the lymphatic afferent circulation and will probably result in acceptably high false negative rates. However, there is almost complete absence of evidence and these are cancers that have been traditionally treated with primary systemic therapy, which means that upfront sentinel lymph node biopsy, in this setting, should not be performed outside the environment of a clinical trial, and inversely speaking, in this setting, if we have to decide to go for upfront surgery for a T4 tumour, for example, what is evidence-based supported is that we should be considering upfront axillary dissection, and, in order to avoid it, we should be discussing into the intra-multidisciplinary environment of the multidisciplinary meetings. Moving further to the special category of male breast cancer, we should start by acknowledging that male breast cancer has been understudied. There is not enough dedicated research that has to do with the low prevalence of it. So, we have been extrapolating from breast cancer trials that have to do mostly with female patients. However, a recent meta-analysis of real-world data and cohort studies have shown that the detection rate is a very high one and the pooled false negative rate is also acceptably low and comparable to that of sentinel lymph node dissection in women. This means that clinical practise complies more or less with the fact that a

male patient with breast cancer that has a negative axilla could undergo sentinel lymph node biopsy. Pregnancy is also a hot and controversial topic, but we know that from the available evidence that is only cohort studies, we could perform surgery during pregnancy, and if the patient is node-negative, we could perform a sentinel lymph node biopsy, however, without the use of blue dye because of its teratogenic effects. So, the current recommendation is that a low dose of isotope is safe for the foetus and sentinel lymph node dissection may be safely performed with accurate results. Moving further to the scenario of ipsilateral in-breast recurrence, there is also lack of randomised controlled trials, but from the available evidence that stems from cohort studies and meta-analysis of these cohort studies, we know that the detection rate on scintigraphy is approximately 60.3% because an ipsilateral in breast cancer recurrence probably suggests that patients have been previously treated with, apart from breast surgery, axillary surgery that was either sentinel lymph node biopsy or axillary dissection. The intraoperative detection rate is at about 60% as well, and the odds ratio for a successful detection is in favour of a previous sentinel lymph node dissection versus axillary lymph node dissection, with an odd ratio being about 3. These patients, however, will be found to have aberrant drainage in approximately 26% of cases, and the aberrant drainage is usually more common in patients that have undergone axillary lymph node dissection instead of sentinel lymph node dissection with an odd ratio that suggests a fourfold difference. Regarding risk factors for a failure post breast-conserving surgery, we have identified radiotherapy, subareolar tracer injection, and the 2-day protocol of technetium injection to be failure factors. On the other hand, we have seen that the axillary recurrence rates after an unsuccessful redo sentinel lymph node dissections are low and the data from the SNARB group from the Netherlands suggest that if one performs staging, which is the way to go if you have a recurrence, I do a parenthesis and say that approximately one out of four to one out of three patients with an in-breast cancer recurrence will be shown to have metastatic disease, which means that staging should be viewed as almost mandatory in these cases. So, if one performs a positron emission tomography in that setting that does not show any axillary disease, performing or not performing sentinel lymph node dissection will not probably affect survival. This suggests that the notion that we could omit axillary dissection in these patients if the PET does not show anything or if standard radiological assessment does not show anything and sentinel lymph node dissection in the redo setting fails, is probably safe for these patients because it is systemic treatment that is the important, especially in this setting. Moving on to a hot and one of my favourite topics, we should discuss sentinel lymph node dissection or any axillary surgery, for that matter, in a preoperative diagnosis of pre-invasive breast cancer, DCIS or pleomorphic LCIS. Let's go for some facts on DCIS. So, we all know that patients with a preoperative diagnosis of DCIS will be found to have upgrade to invasive cancer once the specimen is examined by the pathologist by approximately 25%. This number is ranging depending on reporting series from 15 to 30%. However, the risk for sentinel lymph node metastasis in pure DCIS is very low, up to 0.7%, and mostly attributed to the fact that some metastatic or micro-metastatic focus has been lost during the pathological examination. That risk historically has been known to rise to 9% if we have known microinvasion or core biopsy. But looking into further data in these practise advances, the better we sample the area, the less the upgrade risk seems to be. So, we know from retrospective data that vacuum-assisted biopsy can lower the risk for invasion to 11%. On the other hand, in large DCIS lesions, the use of vacuum-assisted biopsy did not show to reduce that upgrade afterwards. So, this is not very, very conclusive and necessarily helpful. On the other hand, we know from older meta-analysis but also more recent meta-analysis published last year by the EUSOBI that routine MRI for DCIS will not improve outcomes as it has not been shown to be sensitive for the existence of underlying invasive focus. Several small studies have also looked into the outcomes of the dedicated breast positron emission tomography with some conflicting results, but currently, we are not at the point where we should say that any patient with DCIS should undergo dedicated breast PET in order to see if there is underlying invasion. And finally, let's discuss on some more facts on DCIS. The literature has approximately 50 different retrospective studies that are mostly institutional and have developed predictive nomograms on the risk of invasion. In all these studies, size with different cut-offs, either 4 or 5, or 3 cm, grade 2 and 3, so intermediate- and higher-grade DCIS, the presence of comedo necrosis, mass effect, microinvasion, or suspicious microinvasion on biopsy have been shown to be risk for

invasions, but once you remove all the low-risk DCIS, so the grade ones, the small ones and so on, these nomograms do not retain prognostic significance, which suggests that the high-risk DCIS is something that is very hard to predict and decide on whether to perform axillary mapping in the upfront setting for that. So, what does it matter? The short version, the short answer is no. It does not matter because only the presence of invasive cancer, and nowadays, not every invasive cancer, should mandate sentinel lymph node dissection. So, what happens with the pure DCIS node-positive patients? So, that small subcategory. We have seen in large series from the SEER database that axillary evaluation in DCIS will affect treatment but not overall survival and at the same time, we know that axillary evaluation in DCIS will increase complications and long-term morbidity regardless of the procedures that we will be performing. Here we have to highlight the fact that axillary lymph node dissection has no position in the treatment of DCIS as it is, by definition, over-treatment, and failure to detect the sentinel lymph node, if you decide to do it upfront or after previous breast conservation, should not prompt axillary lymph node dissection. So, in general, the rationale to do it upfront is to prevent going back to the fear that in patients with either high-risk of underlying invasion, despite the definition being rather vague, or if the previous breast procedure precludes safe axillary mapping, meaning predominantly mastectomy and the rationale to not do it upfront is because it is not biologically necessary and it is deemed feasible afterwards in most cases. But moving on, we know that sentinel lymph node can safely be omitted in patients with DCIS planned for breast-conserving surgery, but this is not the exact truth, not in any BCS. And what are the facts about that? The only dedicated study until now that looked into the outcomes of sentinel lymph node detection post a recent excision for DCIS was the multi-centre data study from France where they showed a detection rate at reoperation of only 85.5%, with a use of a double-tracer and scintigraphy. Moreover, there is no data on feasibility and the accuracy of sentinel lymph node dissection after oncoplastic breast-conserving surgery, and this is normal because oncoplastic breast-conserving surgery means that you will perform much more extensive dissection, you will move the breast parenchyma significantly more, or you would remove a significant part of the breast and replace that volume with a perforator flap or something similar that will disrupt the lymphatics. So, there is a discussion about that too that is emerging recently. Looking into the risk factors for sentinel lymph node failure in this setting, the previous excision is known to be a risk factor, a large excision will increase the false negative rate, and periareolar incision has shown to increase failure and false negative rate. And from the GATA study, the negative scintigraphy, the use of a single tracer, or reoperation within 36 days, where the oedema is more pronounced and the scar tissue more rigid, was also a sentinel lymph node detection failure factor. What about the guidelines? So, the guidelines do not give always clear recommendation. And these are the outcomes of a systematic review that we did some years ago where apart from mastectomy, we do not have any other consensus, and all the other risk factors are very heterogeneous. So, when these guidelines are used as diagnostic accuracy tools, we see that the way that they behave are completely different. The intraobserver variability, so, how they are interpreted by different medical oncologists, radiation oncologists or surgeons, is very different and at the same time, the area under the curve that is their accuracy, their diagnostic accuracy, is close to 50%, which more or less is the toss of a coin. So, this means that we need a new way of thinking to come around that. Let's just move on with the absence of level 1 evidence and what we do on the context of refraining from sentinel lymph node dissection in invasive breast cancer. So, there is one Italian RCT that compared nothing to axillary dissection for negative axilla, and the results of the SOUND randomised controlled trial that are currently pending. All these studies that are discussing the omission of sentinel lymph node dissection have included mostly patients with T1 tumours and node-negative clinically. The outcomes have not suggested the survival benefit and the axillary recurrence from the INT09/98 trial at 10 years was 9% only. A recent Swedish cohort study with 15-years follow-up where half of the patients had adjuvant radiotherapy, 6.3 had only tamoxifen, only 5.6 had radiotherapy and tamoxifen, and none, 31.6, so one-third of patients did not get any adjuvant treatment, suggested that the breast cancer-specific survival was 94%, the axillary recurrence was low, and the use of adjuvant treatment was non-specific. This is more or less in line with the Choosing Wisely campaign in the USA where it is felt that ER-positive cancers, smaller cancers in ladies that are older than 65-years-old and will receive adjuvant

radiotherapy and endocrine therapy, can refrain from sentinel lymph node biopsy. Just a reminder, feel free to ask your questions, and let's take a breath. Now, so, how to plan and how to perform sentinel lymph node dissection? There are anatomical considerations, there are technical considerations, and there are strategy modifications in challenging situations. Most of you, I guess, are aware of the concept. So, we inject the tracer in the breast that will follow the afferent lymphatics and land in the first nodes that will receive the lymph from the breast. These nodes are identified during surgery, and they are examined by the pathologist. Now, with regards to the anatomy, we have traditionally been discussing about level 1 in the axilla, which is lateral of the pectoralis minor muscle, and level 2, which is behind, and then level 3 which corresponds to what we call infraclavicular lymph nodes. However, the group of Krishna Clough, back in 2010, suggested another classification that was based on an anatomical crossing in the axilla by two anatomic components, the lateral thoracic artery and vein, and the intercostobrachial nerve. So that divided the axilla into four zones, more or less. So in zone A, approximately 87% of times, the sentinel node was situated there, and in zone B, 11.5% of times. So, more or less, we could safely say that in the majority of cases, the sentinel node is expected to be found medial to the lateral thoracic vein and caudally to the second branch of the intercostobrachial nerve which suggests that unnecessary lateral dissections should be probably avoided because they will almost always harm. We have been using the isotope and the blue dye as standard of care for many years because of their high accuracy, but there are also challenges with that. The current status of knowledge is that the detection rates are very high, we are talking about probe-based detection and visual aid-based detection, and have been considered as the standard of care. Recently, the multi-centre, SenSzi randomised clinical trial, showed that in this upfront setting, no scintigraphy was required in order to perform accurate sentinel lymph node biopsy, and we have to reserve it only in other cases, such as that of in-breast recurrence and redo sentinel lymph node biopsy. However, the limited access to radioisotope as well as the allergenic reactions of the blue dye together with discoloration and skin necrosis have prompted the research for new alternatives. These novel tracers are mainly three. The Contrast Enhanced Ultrasound with Microbubbles, the Indocyanine Green, and the Super Paramagnetic Iron Oxide Nanoparticles, and we will be shortly touching up on these. So, the contrast-enhanced ultrasound is based on the notion that a periareolar injection of contrast with microbubbles is administered and then, an ultrasound is performed. So, we identify the uptake in the nodes in the axilla, we identify the nodes, and then, we can easily perform a biopsy of these nodes transcutaneously or mark them with a clip or a wire in order to find them during surgery. The outcomes of that, when one compares it with the isotope, suggests that it has a slightly worse detection rate and the studies are characterised by very, very high heterogeneity. And there is, at the same time, low reproduction and publicity bias. The ICG is based on the principle of the probe and fluorescent camera. So, indocyanine green is injected in the breast, and with a fluorescent camera we are following its course to the axilla where you get a fluorescent lymph node. It allows for real-time lymphography and subsequent sentinel lymph node retrieval. In meta-analysis, we see that the ICG has comparable detection rate with the isotope, and most of the studies have been well-conducted with low heterogeneity and low publication bias. Another characteristic of the ICG, however, is that if we move forward and look into the sentinel lymph node retrieval, we see that it will remove many more sentinel lymph nodes and there is very, very high heterogeneity in these studies, raising the two questions. The one is, is the high detection rate a consequence of the fact that you will retrieve many more nodes? And the other, do we retrieve unnecessarily more nodes than what we need? So, do we land in a mini axillary dissection? Most recent studies suggest that the nodal yield may be comparable, so you do not remove that many nodes, but still, this is compatible with the way the ICG works because it is a small molecule with a low molecular weight that will migrate to higher nodal lesions quickly during surgery. At the same time, it has got many other promising uses such as in axillary reverse mapping, or in the case of assessing margins, for example, or perfusion of flaps. Finally, we are talking about the super paramagnetic iron oxide nanoparticles which are based on paramagnetic technology. So, it is probe-based detection with the help of a probe, but at the same time, the spill will stain the node, so, you will identify a node that is very clearly brown. So, it is by itself a dual tracer as it enables probe-based detection and visual aid-based detection at the same time. At the same time, it resides in the tissue for a longer period of time,

which suggests that preoperative injection is feasible in this setting. In meta-analytical outcomes, the detection rate is completely comparable to the isotope with or without blue dye, and most of the studies have been well-conducted with none to low heterogeneity. With regards to SPIO and sentinel lymph node retrieval, the detection rate seems to be comparable and it is felt that this is kind of safe because you do not land in the excess removal of lymph nodes in this setting. So, SPIO has this very clear advantage of modifying the process but one should not forget the fact that it can stain if not injected peritumorally, and if not removed, then, you would want to do a post-operative MRI, you may encounter artefacts. So, to sum it up, how to do upfront sentinel lymph node? The golden standard according to the literature is the double tracer or any equivalent or non-inferior alternative. Scintigraphy is not necessary in the upfront setting. You should always be aware of the anatomy, and to try to remove the true sentinel lymph node first. The true meaning, the node that you have been able to detect with a tracer that you have used. Palpable nodes do not denote pathologic, despite the fact that most surgeons, we will have a tendency to remove a node if we feel that it is enlarged, hard or fibrotic. You have to consider that the optimal yield for a low false negative rate is more than 2, but no more than 5 because otherwise we are increasing the risk of complications and morbidity. When to do sentinel lymph node in ductal carcinoma in situ? There is unanimous consensus with regards of mastectomy and breast-conserving surgery that will preclude safe lymphatic mapping. However, the true answer is that you should not do it and new emerging methods that I will not touch upon in detail because I'm the primary investigator of the relevant trial, like a preoperative sentinel lymph node marking with SPIO nanoparticles are underway and have given very successful results until now. How to do sentinel lymph node dissection in recurrent breast cancer? For starters, we need to understand whether it is meaningful. So, what about the biology? What about the staging? We should always perform preoperative localization because one-fourth of patients will have extra axillary localization or contralateral axilla. And do not explore axilla out of curiosity. And in the setting that sentinel lymph node dissection fails, if you have a negative staging imaging modality, it is better to do nothing because you do not confer a survival advantage and you will probably not affect the decision for post-operative systemic treatment since this is dictated by tumour biology. Thank you for your attention on the sentinel lymph node dissection matter. I will briefly touch on the fact that axillary lymph node dissection should be reserved to nothing more than clinically positive axilla that have to be treated upfront or advanced breast cancer that, by exception, should be treated also upfront. Nowadays, the role of axillary lymph node dissection, for example, in DCIS, is none, for micrometastatic disease, is none, for up to 2 micrometastases, is none. Thank you very much, and please, let's just start with a stimulating conversation.

Prof Tinterri: Thank you, Andreas, for this nice presentation. Unfortunately, we don't have so much time for the questions, but a quickly question, as regard to the pathological evaluation of the sentinel lymph node, do you feel is it always necessary to perform an intraoperative evaluation or could you recommend also a definitive pathological evaluation?

Prof Karakatsanis: This is a very good and relevant question. So, we know that there are alternatives like imprint cytology, frozen sections, or the OSNA amplification methods, and that would facilitate how we would think about it. On the other hand, we need to make definitive decisions, and since in the setting of all this current knowledge, we need to have a discussion at the multidisciplinary meeting, it feels like this is not mandatory. Let's not forget the very typical example of 15% of our patients that will have lobular breast cancer where a frozen section or even the OSNA may not give us the exact answer that we were expecting. And unfortunately, the literature suggests not only false negatives but also false positives, which means that we may lead the patient to an unnecessary axillary lymph node dissection in this matter. So, the decision should be based on logistics, availability but also in patient case per case.

Dr Kaidar-Person: I fully support your approach, especially since we have data also from Z0011 and AMAROS trial, that even if we have patients with positive sentinel lymph nodes, it's not necessarily that we need to move on to dissection.

Prof Tinterri: Thank you. Andreas, there are some questions from the people of webinar. The first question is, what about extracapsular lymph node metastases? You think this is an indication for axillary dissection also in the lymph node sentinel?

Prof Karakatsanis: So, I think that the literature on the trials that have been performed has looked into that, and extracapsular invasion may or may not be a reason to discuss other treatments, but it does not upgrade. So, a macrometastasis in 3 retrieved sentinel lymph nodes is not more dangerous if it has got extracapsular invasion in the sense that it will mandate surgery. It may or may not, based on institutional practise and patient-related factors, motivate discussion about systemic therapy, for example, or discussing perhaps enhanced locoregional therapy in some cases. But still, there is no consensus that this should prompt axillary dissection instead of sentinel lymph node biopsy.

Prof Tinterri: Orit, what do you think about this?

Dr Kaidar-Person: I fully agree. There is some data to suggest that when you have a focal extracapsular not less than 2 mm but more than 2 mm extracapsular extension, some studies suggest that it is associated with additional tumour burden within the axilla, but it is a consideration also for maybe more intense systemic therapy. We don't know that completely, but I fully agree with this approach.

Prof Karakatsanis: So, if I were to specify, for example, I would discuss going back for an axillary dissection if I had performed sentinel lymph node biopsy, if I had retrieved two sentinel lymph nodes, and two out of two had macro-metastases with extracapsular invasion, this is something that you would need to consider or discuss it with the radiation oncologist and the patient in order to understand if we decide to benefit on that. Let's not forget at the same time that we are talking about upfront surgery setting, which means that, for example, let's just suppose the notion that you would have a post-menopausal woman with an ER-positive HER2-negative breast cancer that has a low-risk genomic score that would fall under the RxPONDER criteria. I think that we would consider chemotherapy in this setting if we had additional risk factors.

Dr Kaidar-Person: Sorry, how do you relate to tumour deposit within the axillary fat? So, we sometimes don't know exactly if it's replaced, the whole lymph nodes, if we don't have residual lymphatic tissue, but how do you consider that?

Prof Karakatsanis: This is a very, very interesting question. Unfortunately, there is no detailed evidence to support any decision in an algorithmic manner. But what I would say is that nowadays, and especially in Europe where, you know, the standard policies to perform an axillary ultrasound at baseline, it is very rarely that an experienced breast radiologist will miss a node that has been completely replaced. So, most of the times, we usually know that this is a node-positive patient and we would not consider a standard sentinel lymph node approach in that. Now, the decision on whether to do fast-track axillary lymph node dissection or proceed with neoadjuvant therapy is something that depends on biology and patient-related factors, of course. But you are making a very, very fair point and this is a point where the literature is not 100% in consensus.

Prof Gentile: Thank you, Andreas. We have another question from the public. It's a very tricky question because what would we do, we surgeons, do in case of narrow ability of the sentinel lymph node? I mean, it's a very rare situation, but still, the guidelines recommend for a complete axillary dissection, in this case, what will we do?

Prof Karakatsanis: So, I will tell you what I routinely do, and I will also tell you when do I make an exemption. I think that we are in full agreement when we say that T4 cancers, formally locally advanced breast cancers, or inflammatory breast cancers, if they are non-metastatic and we want to treat them with a therapeutic intention, we should give preoperative systemic therapy because it has to do with, you know, a very high-risk patient that needs the therapy and the upfront surgery will be more often more extensive, more morbid,

will lead to delays in the adjuvant systemic therapy and so on. So, if I have a T4 tumour, that needs to be operated on, primarily, I will explain the evidence and I will probably go for an upfront axillary lymph node dissection. The only cases that you could do an exception to that and discuss sentinel lymph node biopsy but with a very low threshold of reacting more, is that if you have performed staging, which many perform for T4 tumours, and you have a PET that suggests that the disease is localised only in the breast and nowhere else. But this has to be discussed in the multidisciplinary setting, of course, that's the one thing, and the patient has to be informed that this is not what is currently considered standard of care according to available evidence.

Prof Gentile: Thank you very much. Orit, do you have something to say about that?

Dr Kaidar-Person: I fully agree with what he said, so yeah.

Prof Gentile: Thank you. I think we have the last question. It's about the indocyanine green tracer. We don't use it much, actually. We don't have much experience. And the question is, where to inject the indocyanine green tracer? I think the answer is based on the tumour. If it's a palpable tumour, I think the best option is to inject it around the tumour. In the other hand, if the tumour is not palpable, I think the best option will be to inject the indocyanine green in the subdermal in the periareolar complex. What technique do you use? The microphone is off.

Prof Karakatsanis: Yes. So, I do not personally use indocyanine green systematically. I use super paramagnetic iron oxide nanoparticles, SPIO. But with regards to indocyanine green, the literature is based on studies that advocate a subareolar injection regardless of whether the tumour is palpable, non-palpable, multifocal, or unifocal. The reason for that is that indocyanine green will run fast through the lymphatics. So, you can do an intraoperative injection, you can do some massage and the real-time lymphography, and will land. Then, indocyanine green is a very effective method, at least, this is what the literature suggests, but the potential pitfalls with the technique, as reported in the literature, are three. The first one is that it is a fast wash-in, fast wash-out. So, if you do not find the node the first 20 to 30 minutes because of anatomical challenges or because you have started with breast surgery first, for example, you would probably need to repeat the dose. The other pitfall is that if while dissecting the axilla you transect one of the afferent lymphatics, then you have spillage in the field, which means that instead of a very beautiful fluorescent signal, you get green overall, and when you open the camera, everything is bright. So, that can be challenging. And the third one is the one about sentinel lymph node retrieval, which is what I think is most important because landing in a situation where you remove eight lymph nodes is much closer to an axillary lymph node dissection rather than a sentinel lymph node biopsy. However, reassuringly, the literature shows that experienced users can avoid that pitfall. On the other hand, there is no published data on the learning curve and when do you become experienced enough to overcome these problems.

Prof Tinterri: Thank you, Andreas. I think that the time is really, really ending. Orit, you want last some take-home messages for the people? And for Andreas, you or Andreas is the same.

Dr Kaidar-Person: Take home messages. I think this is a very important session that emphasises the importance of a sentinel lymph node biopsy, when to perform it, and how to perform it. And when it seems obvious for many centres that already omitted the axillary lymph node as much as possible in current days, now, we even have an option in certain cases not to perform it routinely also in DCIS and pleomorphic, as he discussed before. So, I think this is a very important session. But maybe, Andreas wants to also emphasise a few things from his...

Prof Karakatsanis: So, my take on that is that we have moved through the years from an era where we believe that axillary surgery had therapeutic value so, we were performing radical and aggressive surgery because we believed that we were offering some type of benefit for the patient.

Dr Kaidar-Person: The Halstedian concept.

Prof Karakatsanis: Exactly. But I think that the data throughout the years is very, very convincing and very, very clear about the fact that the axilla will provide staging information. And if you have a de-novo positive axilla, then, you have to consider that breast cancer is a systematic disease very early on and you should take a step back and stop thinking like the surgeon who will operate but like the physician that wants to cure. So, you should need to stage and so on. Nowadays, looking at the biology is more important than the knife. And at the same time, we know that if we are to offer surgery of any type in the axilla, it should be mandated by a very, very clear clinical question that is relevant to the case of each patient. This is the case, for example, for the DCIS, this is the case for low-volume metastatic disease in the axilla. I think what I would like to kind of leave from all the data that I presented is what I find very fascinating is that now we have a constellation of randomised controlled trials that have been looking into the concept of low-volume axillary disease. And they are trials that have been designed in a different manner, conducted equally well, but with different patients, in different scenarios and perhaps, in different settings. The fact that the results are very, very similar both with regards to the oncological outcomes on the one hand and on the other hand on how deleterious is aggressive surgery on the quality of life and morbidity are very, very clear and suggest that the way to move forward and to kind of expand on these trials in order to be able to touch on particular patient subgroups that have not been dedicatedly studied upon before is even more important. So, we should refrain from, you know, being trigger-happy. This is my take-home message.

Prof Tinterri: Thank you, Andreas.

Prof Karakatsanis: Thank you very much.

Prof Tinterri: A very, very good final message. Thank you at all, and thank you to ESO for this very, very interesting session. Bye-bye. Ciao!