Uncertainties and Controversies in Axillary Management of Patients with Breast Cancer

Phase 1 of the OPBC 2022/EUBREAST/Toolbox2 Project

Expert representatives

Walter P. Weber and Peter Dubsky, Jane Shaw, Ursula Ganz-Blättler, Joerg Heil, Florian Fitzal, Zoltan Matrai, Jana de Boniface, Christoph Tausch, Thorsten Kuehn, Maggie Banys-Paluchowski, Rosa di Micco, Nina Ditsch, Sherko Kuemmel, Orit Kaidar-Person, Philip Poortmans, Oreste Gentilini, Michael Gnant

Staff

Martin Heidinger, Nadia Maggi

Aim

The aim of phase 1 of the OPBC 2022/EUBREAST/Toolbox2 project is to identify and prioritize uncertainties and controversies based on their importance in contemporary axillary management of patients with breast cancer and to propose concrete strategies to address them.

Definition of importance

Importance is defined as need for evidence-based expert consensus recommendations to standardize international clinical practice.

Background

The OPBC was founded in March 2017 as a global non-profit organization. It became the largest academic network of oncologic, oncoplastic and reconstructive breast surgeons, patient advocates and radiation oncologists from 86 countries with evident expertise in breast cancer management with a practice primarily dedicated to breast cancer. The OPBC

specialized in global phase III randomized controlled trials[1-3], as well as systematic processes to identify knowledge gaps[4] and develop recommendations for clinical research and practice. [5,6]

The European Breast Cancer Research Association of Surgical Trialists (EUBREAST) is a non-for-profit organization that was founded in 2018 with the goal to harmonize and coordinate high level international research in the field of breast cancer surgery. Founding members of EUBREAST have initiated and conducted highly ranked international trials on lymph node surgery (BOOG, SENTINA, INSEMA, SOUND, SENOMAC, GANEA 1,2).[7-16] EUBREAST runs currently the EUBREAST 1 and AXSANA (EUBREAST 3) studies. More than 220 sites from 30 countries are actively recruiting patients for EUBREAST studies.

Methods

Modified Delphi process performed by the OPBC and EUBREAST. OPBC coordinators and panellists as well as EUBREAST scientific board members reflect permanent positions within the OPBC and EUBREAST. They were selected and actively recruited based on evident expertise in breast cancer management with a practice primarily dedicated to breast cancer. The OPBC patient advocacy group consists of patients who underwent oncologic breast surgery in the past and volunteered to support the mission of the OPBC. The OPBC radiation oncologists were addressed by the national OPBC coordinators and responded to a call for participation in an OPBC newsletter. The rest of the OPBC membership consists of breast surgeons from various backgrounds and with different levels of experience who decided to join the mission by self-registration on the OPBC website (www.oncoplasticbc.org).
Participants from EUBREAST are either effective members or associate members of one of the network associations (EUBREAST e.V. Germany, EUBREAST ETS Italy) (www.eubreast.com).
For the Delphi process, given the complexity of identifying uncertainties and controversies in clinical practice in the field of axillary management, we a priori plan to recruit a minimum of 100 OPBC and/or EUBREAST members from around the world as key stakeholders, representing a minimum of 90 clinical experts (i.e., surgeons, gynecologists and radiation oncologists) who are responsible for axillary management and 10 patient advocates.
A questionnaire will be sent to all OPBC members assessing their role (surgeon vs radiation oncologist vs patient advocate). Patients will be asked to provide information on their personal history on a strictly volunteer basis (S/p no axillary surgery, sentinel lymph node procedure, axillary lymph node dissection, breast conserving surgery, mastectomy without reconstruction, mastectomy with implant-based reconstruction, mastectomy with autologous reconstruction). Professionals will be asked about their discipline of origin (gynecologist vs

surgeon vs radiation oncologist), years of experience, annual caseload, sex, and type of breast center (private vs public vs academic).
The modified Delphi process will consist of two rounds of electronic questionnaires followed by a virtual (online) consensus meeting. The online consensus conference will involve a group of expert panellists for discussion and voting with live attendance by the OPBC and EUBREAST membership. Responses will be summarized using purely descriptive statistics.

List of uncertainties and controversies

The expert representatives will be tasked with identifying key uncertainties and controversies in contemporary axillary management of patients with breast cancer. We will purposefully refrain from using a systematic literature search as basis for questionnaire development because we want the OPBC and EUBREAST to identify open questions that are relevant in clinical practice based on either absence of conclusive evidence to inform treatment or absence of expert consensus, or both. To identify published literature in the field that might indicate whether an uncertainty or controversy has already been well addressed, two expert representatives will perform a specific PubMed search (search terms will be defined). The same expert representatives will search ClinicalTrials.gov (search terms will be defined) to obtain information on ongoing clinical trials indicating that uncertainties and controversies might be sufficiently addressed in the near future. Their review of all abstracts and full texts of relevant articles will be used by the expert representatives to adjust the questionnaire, which will be sent to all OPBC and EUBREAST members to give feedback and report additional uncertainties and controversies. The expert representatives will finalize the list of uncertainties and controversies according to these comments.

Delphi process

The modified Delphi method will include two rounds of surveys assessing the importance of uncertainties and controversies with anonymized feed-back of results. Importance is defined as need for evidence-based expert consensus recommendations to standardize international clinical practice. The questionnaire will be sent to all patient advocates with explanations and glossary. After each round, two reminders will be sent by email in two-week intervals to optimize response rates. The Delphi process will be coordinated by a facilitator from the Department of Clinical Research at the University of Basel.

- Round 1:

The chairs will send out personalized access links to the electronic round 1 questionnaire to all OPBC members and EUBREAST participants. They are asked to rank the importance of every knowledge gap on a 9-point Likert scale from 1 (not important) to 9 (extremely important) within 2.5 weeks after receipt. A total of two reminders will be sent during that

time. First-round non-responders will be considered to have declined study participation and will not be contacted again for the second round.

- Round 2:

All participants of round 1 will be sent a second personalized access link to the electronic round 2 questionnaire. The round 2 questionnaire will consist of the same list of uncertainties and controversies as in round 1. In addition, the median rating of round 1 will be indicated separately for medical professionals and patient advocates. Participants will then be asked to complete the questionnaire again within two weeks to reprioritize the respective uncertainties and controversies. A total of two reminders will be sent during that time. Feedback from round 1 will be used for all participants that completed round 1 but did not complete round 2. The median importance rating of each topic will be calculated separately for medical professionals and patient advocates. The mean of the Likert ratings of the two groups will then be used for the ranking of uncertainties and controversies. The ranking is determined by descending median Likert rating.

Virtual OPBC and EUBREAST Consensus Conference (online)

Thursday, 1 Sept 2022, 1.00 p.m. - 4.00 p.m. CET

Co-chairs: Walter P. Weber, Michael Gnant and Sherko Kümmel

An expert panel will meet online to discuss the best methods to address the most important uncertainties and controversies. The 15 questions with the highest overall ranking, as well as the top 5 ranked questions from each discipline will be selected for in-depth discussion at the consensus conference. The panel will decide which uncertainties and controversies should be addressed directly by consensus conferences to develop recommendations for clinical practice based on existing evidence or to bridge until conclusive evidence from ongoing studies is expected to be available.[5,6,17,18] In case of absence of ongoing or planned trials or existing/expected conflicting evidence, the OPBC and EUBREAST will consider to add these research priorities to their research agenda and develop specific clinical research projects to generate conclusive evidence. For this purpose, a research question, which addresses the uncertainty/controversy at least in part, will be developed by the expert representatives in PICO (population, intervention, comparison, outcome of interest) format together with a proposal for a trial design. Both PICO research question and proposed trial design will be adjusted according to the discussion during the conference, followed by voting (y/n/abstain) if panel and members consider them suitable to address the uncertainty and/or controversy. Simple majority will be defined by agreement among 51–75% of the panellists and consensus by agreement above 75%.

Amendments

- Selection of most important uncertainties and controversies for in-depth discussion at consensus conference: The 15 questions with the highest overall ranking, as well as the top 5 ranked question from each discipline will be transferred to the consensus conference.

24 July 2022

Figure 1. Timeline

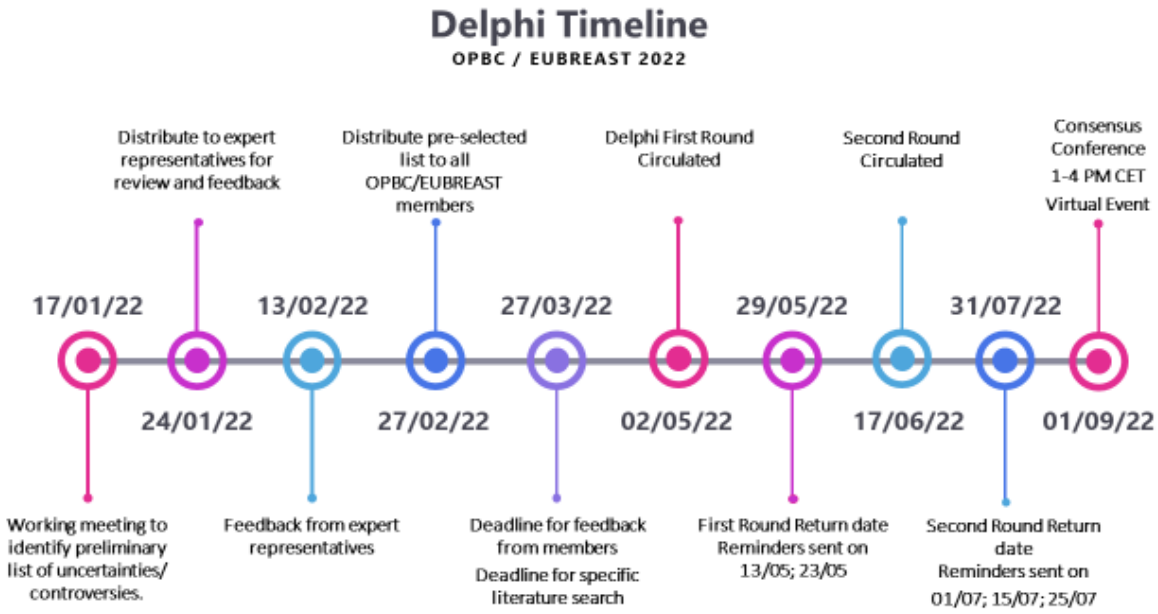
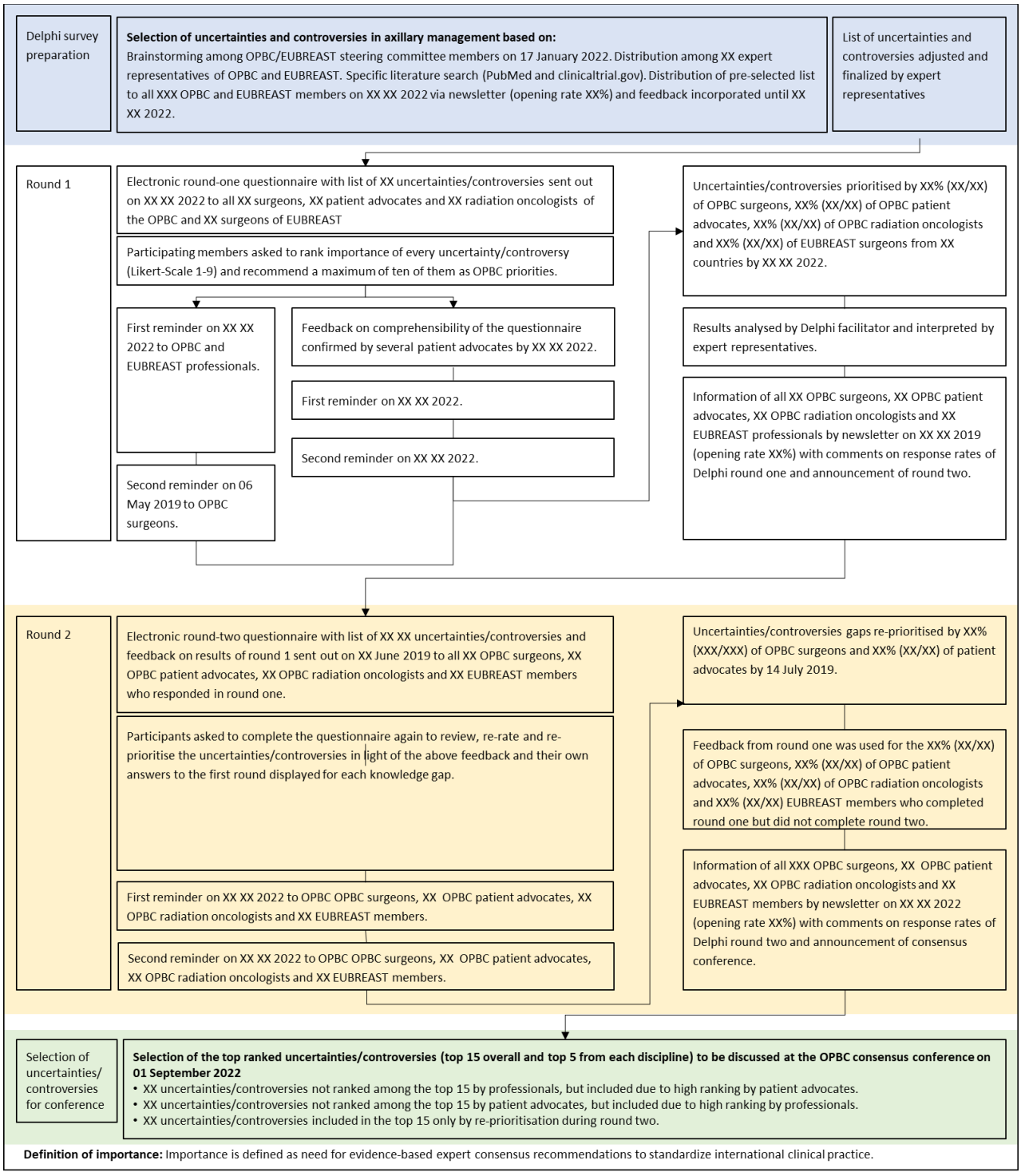


Figure 2. The modified Delphi process



List of Uncertainties and Controversies in Contemporary Axillary Management of Patients with Breast Cancer

Definition of importance during Delphi: Importance is defined as need for evidence-based expert consensus recommendations to standardize international clinical practice.

Session I: Non-invasive staging of the clinically node-negative (cN0) axilla

Contrary to surgical staging (e.g., sentinel lymph node [SLN] procedure) and invasive sampling techniques (e.g., biopsies), non-invasive staging techniques comprise imaging-techniques (e.g., ultrasound [US] and magnetic resonance imaging [MRI]). A clinically node-negative axilla is defined by an unremarkable clinical examination.

1. Should imaging-based staging of the axilla at initial diagnosis and/or after neoadjuvant therapy be standard care and what is the best imaging modality?

Should all patients with breast cancer undergo imaging of the axilla at diagnosis? If a neoadjuvant therapy (a therapy given before the surgical procedure) is undertaken, should imaging of the axilla be standard of care? Additionally, it remains unclear, which imaging modality is best.

2. Should there be development of baseline standards for axillary imaging (e.g., similar to false-negative rates for sentinel lymph node [SLN] procedure)?

Should there be a development towards validation studies, comparing, e.g. different imaging modalities with surgical staging?

3. What is the clinical implication of discordant axillary imaging before surgery (e.g., node suspicious on magnetic resonance imaging [MRI], but not seen on ultrasound [US]?

It remains unclear, how the differing results generated by the different imaging modalities (e.g., US vs. MRI) should be integrated into clinical practice.

Session II: Omission of axillary surgery

Axillary surgery comprises (i) sentinel lumph node (SLN) procedure, (ii) targeted axillary dissection (TAD), which includes SLN procedure and removal of clinically suspicious lymph nodes, and (iii) axillary lymph node dissection (ALND), which is defined as the removal of all lymphoid-tissue of the axilla.

4. Is there an optimal age, size or frailty threshold to omit the SLN procedure?

Are there optimal cut-offs in age, tumor size, and/or frailty (a state of increased vulnerability to stressors, following declines in function and reserves across multiple physiologic systems) to omit the SLN procedure?

5. Should we omit the SLN procedure in a clinically node-negative (cN0) patient with triple-negative (TNBC) or Her-2 positive breast cancer and a high likelihood of pathologically negative nodes after neoadjuvant chemotherapy?

In patients with an overexpression of the human epidermal growth factor receptor 2 (Her-2), or with a triple negative (estrogen receptor negative, progesterone receptor negative, Her-2 negative) breast cancer subtype, a clinically unremarkable examination of axillary lymph nodes, and a neoadjuvant chemotherapy with a high

likelihood of tumor-free lymph nodes in the histological examination (pathologically negative), the question remains, whether we should omit the sentinel lymph node (SLN) procedure?

6. Should we evaluate omission of axillary surgery by delaying the SLN procedure after evaluation of breast pathologic complete response during primary surgery?

Should we evaluate not conducting axillary surgery in patients who receive therapy before surgery by primarily evaluating the therapy-response in surgically removed breast-tissue, and in a delayed second step conduct the SLN procedure, depending on a pathologic complete response in the breast or not?

7. What is the role of axillary surgery in ipsilateral in-breast recurrence after previous breast-conserving surgery and SLN procedure?

What is the role of axillary surgery in patients, who experience an in-breast recurrence in the same breast, which has previously been operated by breast-conserving surgery and SLN procedure?

8. What is standard care in case of aberrant drainage with internal mammary or contralateral axillary SLNs on lymphoscintigraphy in ipsilateral in-breast recurrence after previous breast-conserving surgery and SLN procedure?

How should we proceed in patients, who experience an in-breast recurrence in the same breast, which has previously been operated by breast-conserving surgery and SLN procedure, and show atypical lymphoid drainage to the internal mammary lymph nodes, or the contralateral axillary lymph nodes detected by a special type of imaging known as lymphoscintigraphy?

Session III: Omission of axillary lymph node dissection (ALND) in cN0 SLN+ patients

Axillary lymph node dissection (ALND) is defined as the removal of all lymphoid-tissue of the axilla, including three anatomically defined levels, namely (i) Level I below and lateral the pectoralis minor muscle, (ii) Level II underneath/posterior the pectoralis minor muscle, and (iii) Level III above/medial the pectoralis minor muscle, whereas removal of Level III lymph nodes is only performed upon gross nodal disease with palpation during surgery. Questions remains, in which patients with an unremarkable clinical examination, yet a tumor infiltrated (positive) sentinel lymph node ALND can be omitted.

9. Should the ACOSOG Z0011 protocol considered to be standard care around the world?

In the ACOSOG Z0011 study, patients with a breast cancer up to 5 cm (≤T2) and a clinically node-negative axilla yet 1 or 2 positive sentinel lymph nodes were randomized to receive ALND or no ALND, with all patients receiving lumpectomy of the breast, adjuvant whole-breast radiotherapy and adjuvant systemic therapy. 10-year follow-up results showed no difference in overall survival, disease-free survival, and regional recurrences. Therefore, the question is, whether treatment according to this study-protocol should be standard of care?

10. Should we offer choice between observation (Z0011), axillary radiation (AMAROS) and ALND, or set hard thresholds and if we offer choice should we explore research into shared decision making and informational provision for this choice to support women?

Whilst no further axillary intervention after the SLN procedure was undertaken in the ACOSOG Z0011 study, patients with a breast cancer up to 5 cm and a clinically node-negative axilla yet ≥1 positive sentinel lymph node

were randomized to receive ALND or axillary irradiation in the AMAROS trial. 10-year follow-up results showed no difference in overall survival, regional recurrences and distant metastasis-free survival. Hence, the question remains, whether clinicians should offer patients the choice between those three axillary treatment options, or whether hard thresholds for the respective practice should be set. Furthermore, should we explore research into shared decision making and informational provision for this choice to support women?

11. What is standard care for non-palpable ultrasound-detected lymph node metastases in a Z0011-eligible patient?

In patients with an ultrasound (US) detected positive lymph node, who are therefore clinically node positive but otherwise fulfill all inclusion criteria of the ACOSOG Z0011 study, it remains unclear, what should be standard of care.

12. What is the role of imaging-guided localization and selective removal of non-palpable biopsy-positive or suspicious nodes in the upfront surgery setting?

In breast cancer patients undergoing upfront surgery, what is the role of imaging-guided (e.g., US-guided) localization and selective removal of lymph nodes, which are non-palpable but are either biopsy proven to contain tumor, or which look suspicious on imaging?

13. Should we apply the Z0011 protocol to cN- patients with pathologically positive SLNs who were not eligible for Z0011 (e.g., mastectomy, cT3 cancer, >2 positive SLNs, gross extranodal disease, partial breast or intraoperative radiotherapy)?

The question remains, whether patients, who were not eligible for participation in the ACOSOG Z0011 study (e.g., because they underwent mastectomy, or their primary tumor had a diameter of >5cm, or more than 2 lymph nodes were positive, or tumor cells were detected outside the lymph node in the peri-lymphoid tissue, or who underwent partial breast radiotherapy or intraoperative irradiation), should also be treated according to the ACOSOG Z0011 study protocol?

14. Should we apply the Z0011 protocol to cN- patients with microscopic extranodal extension in SLN metastases?

The question remains, whether patients, who show microscopic tumor cell spread outside of the lymph node in the peri-lymphoid tissue should also be treated according to the ACOSOG Z0011 study protocol?

15. Should the ratio of positive to negative sentinel nodes have an impact on eligibility of the Z0011 protocol (e.g., 2 of 2 versus 2 of 5 removed SLNs are positive)?

It remains unclear, whether the ratio of positive to negative SLN should have an impact on the eligibility of the ACOSOG Z0011 protocol (e.g., should it have an impact if 2 out of 2 SLN are positive, compared to the situation in which 2 out of 5 SLN are positive)?

16. Should tumor biology have an impact on eligibility of the Z0011 protocol?

Should it have an impact on the ACOSOG Z0011 protocol, whether a breast cancer patient has a e.g. hormone-receptor positive breast cancer, compared to a Her-2 positive breast cancer, or a triple-negative breast cancer<?

17. Should invasive lobular breast cancer be managed equally to invasive ductal carcinoma regarding omission of ALND?

Should criteria for the omission of ALND be equally applied in patients with an invasive lobular cancer, compared to patients with an invasive ductal carcinoma?

18. In which non-Z0011 eligible patients should intraoperative frozen section analysis of the SLN be standard care?

In which patients, who do not fulfill eligibility criteria for the ACOSOG Z0011, should a frozen section taken during the primary operation on the SLN be standard of care?

19. What should be standard care in case of nodal disease left behind after axillary surgery and detected by imaging before the end of adjuvant therapy (e.g., PET-CT or planning CT for radiation): biopsy, resect, irradiate as special field or boost, observe, ignore?

The question remains, how to proceed in patients, who underwent axillary surgery, and in which secondary cancers are detected by imaging that takes place during post-operative therapy. Should we take a biopsy, remove, irradiate as special field or boost (i.e. extra radiotherapy on the area of the metastasis), observe or ignore them?

20. What is the contemporary morbidity of the SLN procedure versus ALND and SLN procedure versus no axillary surgery and its impact on quality of life?

What is the disease burden, and impact on the quality of life in patients undergoing the SLN procedure compared to ALND or no axillary surgery?

21. What is the impact of the lack of knowledge of the exact number of positive and negative nodes on use of molecular tests (e.g., Oncotype DX®, Mammaprint®) and adjuvant therapy decisions?

Regarding omission of axillary surgery, the question remains what the impact of our lack of knowledge on the exact number of positive and negative lymph nodes is regarding molecular test and adjuvant treatment decisions?

Session IV: Omission of ALND in patients with clinically node-positive (cN+) breast cancer

22. When will we be able to banish most of the remaining routine indications for radical ALND from clinical practice to improve patient-reported quality of life without jeopardizing survival and oncologic safety (e.g., palpable disease in the adjuvant setting or residual disease in the neoadjuvant setting)?

In, for example, patients showing palpable lymph nodes in the adjuvant setting, or residual disease after neoadjuvant treatment, what needs to be true for us to be able to banish the remaining routine indications for radical Axillary lymph node dissection (ALND) from clinical practice to improve patient-reported quality of life without jeopardizing survival and oncologic safety?

23. What is the exact definition of clinical complete response (ycN0), thus allowing limited axillary surgery (i.e., SLN or TAD) with the aim of omitting ALND?

It remains unclear, how exactly a clinical complete response of the axillary lymph nodes after neoadjuvant treatment (ycN0) should be defined, thus allowing a limited axillary surgery (i.e., SLN or targeted axillary dissection [TAD], which comprises the removal of sentinel lymph nodes as well as pre-neoadjuvant treatment marked positive lymph nodes) and omitting ALND.

24. Should measures to decrease the false-negative rate of the SLN procedure in initially cN+ converting to ycN0 be standard care, such as use of dual tracer or removal of a minimum of 3 negative SLNs?

In patients with breast cancer, who initially present with lymph node metastases, receive neoadjuvant treatment, and clinically do not show tumor cells in the lymph nodes thereafter (ycN0), the question remains, whether measures to decrease the false-negative rate of the SLN procedure, such as dual tracer, or the removal of a minimum of 3 sentinel lymph nodes should be applied?

25. Should targeted axillary dissection (TAD versus SLN only or ALND) be standard care in initially cN+ converting to ycN0 and is TAD oncologically safe compared to ALND?

In patients with breast cancer, who initially present with lymph node metastases, receive neoadjuvant treatment, and clinically do not show tumor cells in the lymph nodes thereafter (ycN0), the question remains, whether targeted axillary dissection (TAD), should be standard of care (compared to sentinel lymph node procedure or Axillary lymph node dissection (ALND), and whether it is oncologically safe?

26. Should use of the SLN or TAD procedures with the aim of omitting ALND in patients with cN+ converting to ycN0 depend on the initial clinical tumor load (e.g., large number of initially suspicious lymph nodes, cN2/3, cT4)?

In patients with breast cancer, who initially present with lymph node metastases, receive neoadjuvant treatment, and clinically do not show tumor cells in the lymph nodes thereafter (ycN0), the question remains, whether TAD or the SLN procedure with the aim of omitting ALND should depend on the initial tumor stage?

27. Should the finding of nodal pCR by use of the SLN or TAD procedure with the aim of omitting ALND in patients with cN+ converting to ycN0 depend on the documentation of regressive changes in the lymph node by the pathologist?

In patients with breast cancer, who initially present with lymph node metastases, receive neoadjuvant treatment, and clinically do not show tumor cells in the lymph nodes thereafter (ycN0), the question remains, whether the definition of a pathologic complete response (pCR) after TAD or the SLN procedure should depend on the visualization of regressive changes in the removed lymph nodes?

28. How many suspicious nodes on imaging should be marked (e.g., clipped) in a patient undergoing neoadjuvant chemotherapy (NACT)?

In patients with breast cancer, who initially present with lymph node metastases, and are planned to receive neoadjuvant treatment, the question remains, how many suspicious lymph nodes should be marked before treatment initiation?

29. Is there a volume threshold of residual nodal disease after neoadjuvant **chemotherapy** (NACT) when radiation can replace ALND (ITC versus

micrometastatic versus macrometastatic residual disease in one or more lymph nodes)?

In patients with breast cancer, who initially present with lymph node metastases and receive neoadjuvant chemotherapy, the question remains, whether we can define a volume threshold of residual nodal disease after surgical lymph node removal in which radiation can replace Axillary lymph node dissection ALND (i.e. isolated tumor cells [ITC], micrometastasis, (Micrometastasisstases are microscopic cancer cells that have escaped from the original tumor and are defined by size. They should be less than or equal to 2mm in largest dimension), macrometastasis (Metastases larger than 2mm), residual disease in one or more lymph nodes)?

30. What is the maximum volume of residual nodal disease after neoadjuvant hormonal therapy (NET) that radiation can control (ITC versus micrometastatic versus macrometastatic residual disease in one or more lymph nodes), thus allowing omission of ALND?

In patients with breast cancer, who initially present with lymph node metastases and receive neoadjuvant hormonal therapy, the question remains, whether we can define a volume threshold of residual nodal disease after surgical lymph node removal in which radiation can replace ALND (isolated tumor cells [ITC], micrometastasis, macrometastasis, residual disease in one or more lymph nodes)?

31. What is standard care for suspicious findings in internal mammary or supraclavicular lymph nodes on imaging?

How should we proceed, if suspicious findings are seen in lymph nodes of the internal mammary or supraclavicular region?

32. What is the best axillary surgery procedure after neoadjuvant radiation therapy?

Session V: Axillary radiation and extended regional nodal irradiation (ERNI)

Axillary radiotherapy is defined as the irradiation of the axilla. Extended regional nodal irradiation (ERNI) includes radiotherapy of the axilla, the supra- and infraclavicular lymph nodes and/or the internal mammary lymph nodes.

33. What is the best nodal irradiation technique?
34. Are there subgroups of Z0011-eligible patients that should receive axillary radiation, and should axillary radiation in Z0011-eligible patients –if indicated- be combined with ERNI (e.g., levels 1-4, levels 3-4, internal mammary nodes, and combinations)?

Should certain Z0011-eligible patients receive axillary irradiation, and should axillary irradiation be combined with ERNI?

35. What is the optimal patient selection for ERNI in general and for specific ERNI protocols in particular (e.g., levels 1-4, levels 3-4, internal mammary nodes, and combinations)?

The question remains, which selection criteria are optimal to select patients for ERNI in general and for specific ERNI protocols.

36. What are the side effects of axillary radiation using modern techniques?

37. What is the risk of lymphedema in a patient who develops recurrence in the axilla after radiation of the axilla and undergoes ALND?
38. In what situations can axillary radiotherapy be de-escalated?

It remains unclear, in which patients/situations axillary radiotherapy can be omitted.

Session VI: Conceptual and technical questions

39. Should intercostobrachial nerves be preserved during ALND?

Intercostobrachial nerves are nerves, which run from the intercostal space to the upper-arm, transmitting sensation and pain, which is why damage to these nerves can cause sensation losses as well as pain.

40. How can we prevent axillary web syndrome?

Axillary web syndrome comprises the formation of postoperative fibrotic cords or bands underneath the armpit, which may also involve the arm.

41. Should lymphatic vessels be preserved during ALND, e.g. by using axillary reverse mapping or stepwise limited ALND?

Axillary reverse mapping (ARM) is a technique where blue dye is injected into the upper arm at surgery, allowing direct visualization of arm lymphatics and nodes during either SLN or ALND.

42. Should level II be included in standard ALND?

The question remains, whether level II lymph nodes (i.e., lymph nodes underneath/posterior the pectoralis minor muscle) should be included in standard ALND?

43. When should level III be included in ALND?

The question remains, whether level III lymph nodes (i.e., lymph nodes above/medial the pectoralis minor muscle) should be included in standard ALND?

44. What is the best tracer to mark sentinel nodes and when should we use dual tracer?

It remains unclear, which tracer is best for the SLN procedure, and when dual tracer (i.e., using two tracing methods as for example Technetium and blue-dye) should be used?

45. What is the best method to mark the sampled node and the best imaging modality to localize it?

It remains unclear, which method is best to mark the sampled lymph node (e.g., clip), and which imaging modality is best to localize it?

46. Should the biopsied lymph node be marked (e.g., clipped) immediately or after histologic confirmation of metastasis?
47. What is the best pathology assessment of the SLN and should it be standardized?
48. Is there a role for nomograms that predict the likelihood of nodal metastases based on patient, tumor and treatment variables in contemporary axillary management?

A nomogram is a predictive tool. These tools are based on information from hundreds or even thousands of people with cancer. The tools can be used to predict cancer outcomes or assess risk based on specific characteristics of a patient and their disease.

Session VII: Follow up

49. What is the optimal follow-up interval and imaging modality for patients after axillary surgery?

How often should we see patients for follow-up, and which imaging modality is optimal for patients after axillary surgery (e.g., sonography, MRI)?

50. How should we address lack of sensitivity of axillary imaging during follow-up?
51. What are the clinically most relevant endpoints in axillary management (survival, recurrence, lymphedema, morbidity, patient-reported outcomes)?

Appendix 1: Questionnaires to assess characteristics of OPBC panelists

2022 Consensus Conference

PERSONAL INFORMATION FORM

PATIENT ADVOCATES

Name (optional): _____

Middle Name (optional): _____

Surname (optional): _____

Affiliation (if applicable): _____

Gender: Female ☐ Male ☐

Year of diagnosis: _____

Surgical procedure (zero, one or more than one response possible):

☐ No axillary surgery

☐ Sentinel lymph node procedure

☐ Axillary lymph node dissection

☐ Breast conserving surgery

☐ Mastectomy without reconstruction

☐ Mastectomy with implant-based reconstruction

☐ Mastectomy with reconstruction using your own body tissue

☐ No surgical treatment

☐ I prefer not to disclose this information

2022 Consensus Conference

PERSONAL INFORMATION FORM

SURGEONS

Name: _____

Middle Name: _____

Surname: _____

Affiliation: _____

_____

_____

Board Certificate: **General Surgery** ☐ **Gynecology** ☐ **Plastic Surgery** ☐

Years of Experience: _____

Estimated Number of Breast Surgery Procedures Performed or Assisted in 2020:

0-20 ☐ 20-50 ☐ 50-100 ☐ 100+ ☐

Gender: Female ☐ Male ☐

Type of Breast Center: Academic ☐ Public ☐ Private ☐

2022 Consensus Conference

PERSONAL INFORMATION FORM

Radiation Oncologists

Name: _____

Middle Name: _____

Surname: _____

Affiliation: _____

_____

_____

Years of Experience: _____

Estimated number of patients with breast cancer treated in 2020:

0-20 ☐ 20-50 ☐ 50-100 ☐ 100+ ☐

Gender: Female ☐ Male ☐

Type of Breast Center: Academic ☐ Public ☐ Private ☐ Not applicable ☐

References

1. Weber WP, Matrai Z, Hayoz S, et al: Tailored axillary surgery in patients with clinically node-positive breast cancer: Pre-planned feasibility substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101). Breast 60:98-110, 2021
2. Henke G, Knauer M, Ribi K, et al: Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials 19:667, 2018
3. Kappos EA, Schulz A, Regan MM, et al: Prepectoral versus subpectoral implant-based breast reconstruction after skin-sparing mastectomy or nipple-sparing mastectomy (OPBC-02/ PREPEC): a pragmatic, multicentre, randomised, superiority trial. BMJ Open 11:e045239, 2021
4. Weber WP, Morrow M, Boniface J, et al: Knowledge gaps in oncoplastic breast surgery. Lancet Oncol 21:e375-e385, 2020
5. Weber WP, Soysal SD, El-Tamer M, et al: First international consensus conference on standardization of oncoplastic breast conserving surgery. Breast Cancer Res Treat 165:139-149, 2017
6. Weber WP, Haug M, Kurzeder C, et al: Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. Breast Cancer Res Treat 172:523-537, 2018
7. van Roozendaal LM, Vane MLG, van Dalen T, et al: Clinically node negative breast cancer patients undergoing breast conserving therapy, sentinel lymph node procedure versus follow-up: a Dutch randomized controlled multicentre trial (BOOG 2013-08). BMC Cancer 17:459, 2017
8. Kuehn T, Bauerfeind I, Fehm T, et al: Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14:609-18, 2013
9. Reimer T, Hartmann S, Stachs A, et al: Local treatment of the axilla in early breast cancer: concepts from the national surgical adjuvant breast and bowel project B-04 to the planned intergroup sentinel mamma trial. Breast Care (Basel) 9:87-95, 2014
10. Reimer T, Stachs A, Nekljudova V, et al: Restricted Axillary Staging in Clinically and Sonographically Node-Negative Early Invasive Breast Cancer (c/iT1-2) in the Context of Breast Conserving Therapy: First Results Following Commencement of the Intergroup-Sentinel-Mamma (INSEMA) Trial. Geburtshilfe Frauenheilkd 77:149-157, 2017
11. Gentilini O, Veronesi U: Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSouND). Breast 21:678-81, 2012
12. Gentilini O, Veronesi U: Staging the Axilla in Early Breast Cancer: Will Imaging Replace Surgery? JAMA Oncol 1:1031-2, 2015
13. de Boniface J, Ahlgren J, Andersson Y, et al: The generalisability of randomised clinical trials: an interim external validity analysis of the ongoing SENOMAC trial in sentinel lymph node-positive breast cancer. Breast Cancer Res Treat 180:167-176, 2020
14. Classe JM, Loaec C, Gimbergues P, et al: Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat 173:343-352, 2019
15. Reimer T, Glass A, Botteri E, et al: Avoiding Axillary Sentinel Lymph Node Biopsy after Neoadjuvant Systemic Therapy in Breast Cancer: Rationale for the Prospective, Multicentric EUBREAST-01 Trial. Cancers (Basel) 12, 2020
16. Banys-Paluchowski M, Gasparri ML, de Boniface J, et al: Surgical Management of the Axilla in Clinically Node-Positive Breast Cancer Patients Converting to Clinical Node Negativity through Neoadjuvant Chemotherapy: Current Status, Knowledge Gaps, and Rationale for the EUBREAST-03 AXSANA Study. Cancers (Basel) 13, 2021
17. Dubsky P, Pinker K, Cardoso F, et al: Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. Lancet Oncol 22:e18-e28, 2021

18. Weber WP, Shaw J, Pusic A, et al: Oncoplastic breast consortium recommendations for mastectomy and whole breast reconstruction in the setting of post-mastectomy radiation therapy. Breast 63:123-139, 2022