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Controversy

Uncertainties and controversies in axillary management of patients with breast cancer

Walter P Weber [a,b,1,*], Oreste Davide Gentilini [c,1], Monica Morrow [d], Giacomo Montagna [d], Jana de Boniface [e,f], Florian Fitzal [g,h], Lynda Wyld [i,j], Isabel T. Rubio [k], Zoltan Matrai [l], Tari A. King [m], Ramon Saccilotto [b,n], Viviana Galimberti [o], Nadia Maggi [a,b], Mariacarla Andreozzi [a,b], Virgilio Sacchini [d], Liliana Castrezana López [p], Julie Loesch [q], Fabienne D. Schwab [a,b], Ruth Eller [a,b], Martin Heidinger [a,b], Martin Haug [a,b], Christian Kurzeder [a,b], Rosa Di Micco [c], Maggie Banys-Paluchowski [r], Nina Ditsch [s], Yves Harder [t,u], Régis R. Paulinelli [v,w], Cicero Urban [x], John Benson [y,z], Vesna Bjelic-Radisic [aa,ab], Shelley Potter [ac], Michael Knauer [ad], Marc Thill [ae], Marie-Jeanne Vrancken Peeters [af,ag], Sherko Kuemmel [ah,av], Joerg Heil [ai], Bahadir M. Gulluoglu [aj], Christoph Tausch [ak], Ursula Ganz-Blaettler [al], Jane Shaw [am], Peter Dubsky [au,an], Philip Poortmans [ao], Orit Kaidar-Person [ap,aq,ar], Thorsten Kühn [as,1], Michael Gnant [h,at,1]

[a] Breast Center, University Hospital Basel, Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Breast Surgery, San Raffaele University and Research Hospital, Milan, Italy
[d] Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[e] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[f] Department of Surgery, Breast Unit, Capio St Göran's Hospital, Stockholm, Sweden
[g] Department of General Surgery, Division of Visceral Surgery, Medical University Vienna, Austria
[h] Austrian Breast and Colorectal Study Group ABCSG, Vienna, Austria
[i] Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
[j] Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, Doncaster, UK
[k] Breast Surgical Oncology Unit, Clinica Universidad de Navarra, Madrid, Spain
[l] Hamad Medical Corporation, Dept of Oncoplastic Breast Surgery, Doha, Qatar
[m] Division of Breast Surgery, Brigham and Women's Hospital, Dana Farber/Brigham Cancer Center, Boston, MA, USA
[n] Department of Clinical Research, University Hospital Basel, Basel, Switzerland
[o] Istituto Europeo di Oncologia, IRCCS, Milan, Italy
[p] Interdisciplinary Breast Center, Cantonal Hospital Baden, Baden, Switzerland
[q] Gynecology Department, University Hospital Zurich, Zurich, Switzerland
[r] Department of Gynecology and Obstetrics University Hospital Schleswig-Holstein Campus Lübeck, Lübeck, Germany
[s] Department of Gynaecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany
[t] Department of Plastic, Reconstructive and Aesthetic Surgery, Ospedale Regionale di Lugano, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland
[u] Faculty of Biomedical Sciences, Università Della Svizzera Italiana, Lugano, Switzerland
[v] Federal University of Goias, Goias, Brazil
[w] Breast Unit, Araújo Jorge Hospital, Goias, Brazil
[x] Breast Unit, Hospital Nossa Senhora Das Graças, Curitiba, Brazil
[y] Cambridge Breast Unit, Addenbrooke's Hospital Cambridge, Cambridge, UK
[z] Cambridge Breast Unit, Cambridge University Hospitals NHS Foundation TRUST, School of Medicine, Anglia Ruskin University, Cambridge, UK
[aa] Breast Unit, University Hospital Helios Wuppertal, University Witten/Herdecke, Wuppertal, Germany
[ab] Medical University Graz, Graz, Austria
[ac] University of Bristol, Medical School, Bristol, UK
[ad] Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland
[ae] Department of Gynaecology and Gynaecological Oncology, Agaplesion Markus Krankenhaus, Frankfurt am Main, Germany
[af] Department of Surgery, Netherlands Cancer Institute, Amsterdam, Netherlands
[ag] Department of Surgery, University Medical Center, Amsterdam, Netherlands
[ah] Breast Unit, Hospital Essen-Mitte, Germany

* Corresponding author at: University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland.
E-mail address: walter.weber@usb.ch (W.P. Weber).

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[ai] Department of Obstetrics and Gynecology, University of Heidelberg, Medical School, Heidelberg, Germany
[aj] Marmara University School of Medicine, Istanbul, Turkey
[ak] Breast Center Zurich, Zurich, Switzerland
[al] University of St, Gallen, St. Gallen, Switzerland
[am] Patient Advocacy Group, Oncoplastic Breast Consortium, Basel, Switzerland
[an] University of Lucerne, Faculty of Health Sciences and Medicine, Lucerne, Switzerland
[ao] Iridium Netwerk and University of Antwerp, Wilrijk-Antwerpen, Belgium
[ap] Breast Cancer Radiation Therapy Unit, at Sheba Medical Center, Ramat Gan, Israel
[aq] Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[ar] GROW-School for Oncology and Reproduction, Maastricht University Medical Centre, Dept. Radiation Oncologv (Maastro), Maastricht, Netherlands
[as] Department of Gynecology, Hospital Esslingen, Esslingen, Germany
[at] Comprehensive Cancer Center Medical University Vienna, Vienna, Austria
[au] Breast Centre, Hirslanden Clinic St. Anna, Lucerne, Switzerland
[av] Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

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ABSTRACT

The aims of this Oncoplastic Breast Consortium and European Breast Cancer Research Association of Surgical Trialists initiative were to identify uncertainties and controversies in axillary management of early breast cancer and to recommend appropriate strategies to address them. By use of Delphi methods, 15 questions were prioritized by more than 250 breast surgeons, patient advocates and radiation oncologists from 60 countries. Subsequently, a global virtual consensus panel considered available data, ongoing studies and resource utilization. It agreed that research should no longer be prioritized for standardization of axillary imaging, de-escalation of axillary surgery in node-positive cancer and risk evaluation of modern surgery and radiotherapy. Instead, expert consensus recommendations for clinical practice should be based on current evidence and updated once results from ongoing studies become available. Research on de-escalation of radiotherapy and identification of the most relevant endpoints in axillary management should encompass a meta-analysis to identify knowledge gaps, followed by a Delphi process to prioritize and a consensus conference to refine recommendations for specific trial designs. Finally, treatment of residual nodal disease after surgery was recommended to be assessed in a prospective register.

Introduction

Management of the axilla in patients with early breast cancer (BC) has undergone major changes in the last few years due to multimodality approaches and the declining status of axillary surgery as a staging procedure. This process of surgical de-escalation began when sentinel lymph node (SLN) biopsy replaced axillary lymph node dissection (ALND) as standard of care in patients with node-negative breast cancer [1]. The progressive reduction of surgical intervention continues following publication of practice changing trials, such as ACOSOG Z0011, IBCSG 23-01 and EORTC AMAROS [2–5]. ALND remains standard of care for patients with clinically node-negative BC with positive SLNs who do not meet the eligibility criteria of these trials, and for patients with clinically node-positive BC in the upfront surgery setting and with residual nodal disease after primary systemic therapy (PST). Whilst results of these seminal trials raised additional research questions which are being addressed in ongoing clinical trials, they also led to much variation in routine clinical practice [6–13]. These rapidly evolving changes in our knowledge base have created challenges in management for certain clinical scenarios such as axillary treatment after PST. Strategies require a collective international effort with the aim of identifying knowledge gaps, addressing uncertainties and planning a new generation of clinical trials to ensure optimal resource utilization.

The Oncoplastic Breast Consortium (OPBC) and European Breast Cancer Research Association of Surgical Trialists (EUBREAST- network) are international non-profit organizations committed to standardizing surgical procedures and supporting international clinical research in the field of breast cancer surgery [12–20]. The aim of this first joint venture was to prioritize important controversies in axillary management, to determine issues that should directly be forwarded to clinical practice guideline development, e.g. by the "Lucerne Toolbox" or OPBC consensus conferences, and to identify appropriate study designs for major knowledge gaps [14,16,17,21].

Methods

Collaborative study groups

The OPBC was founded in March 2017 as a global non-profit organization and rapidly became one of the largest academic networks of loco-regional BC specialists and patient advocates with currently 782 members from 90 countries [22]. The OPBC aims at improving breast cancer surgery by performing research and clinical practice guideline development projects. It has a particular interest in global phase III randomized controlled trials and other multicenter studies, as well as systematic processes aimed at identifying knowledge gaps with development of recommendations for research strategies that optimize clinical practice [12–20].

EUBREAST- network is a group of independent non-for-profit organizations founded in 2018 whose goal is to harmonize and coordinate high level international research in the field of breast cancer surgery with a focus on less extensive approaches in order to improve patients' quality of life. The EUBREAST Network is represented in over 30 countries, with a direct reach to about 1500 medical professionals (including approximately 200 members/associates and 275 active principal investigators). Founding members of EUBREAST- network have promoted and conducted key international trials on lymph node surgery (BOOG, SENTINA, INSEMA, SOUND, SENOMAC, GANEA 1,2) and the organisation currently oversees the EUBREAST 1 and AXSANA (EUBREAST 3) studies. [23–32].

List of uncertainties and controversies

Identification of uncertainties and controversies was achieved by adherence to a pre-specified protocol (see supplementary appendix 1). First, expert representatives were tasked with identifying key uncertainties and controversies in contemporary axillary management of

[1] Contributed equally.

breast cancer patients that are pertinent to routine clinical practice but for which there is a lack of conclusive evidence and/or expert consensus to inform treatment. A review of abstracts and full texts of relevant articles from a focussed literature search was used by expert representatives to amend this list of uncertainties and controversies. A refined list was sent to all 703 OPBC and the selected EUBREAST- network members who provided feedback and highlighted areas of additional uncertainty and controversy. Expert representatives then finalized the list of uncertainties and controversies based on these comments from OPBC and EUBREAST-network members.

Search strategy and selection criteria

Instead of a systematic literature search including several large citation databases as basis for questionnaire development, a specific search of PubMed and ClinicalTrials.gov was performed by two expert

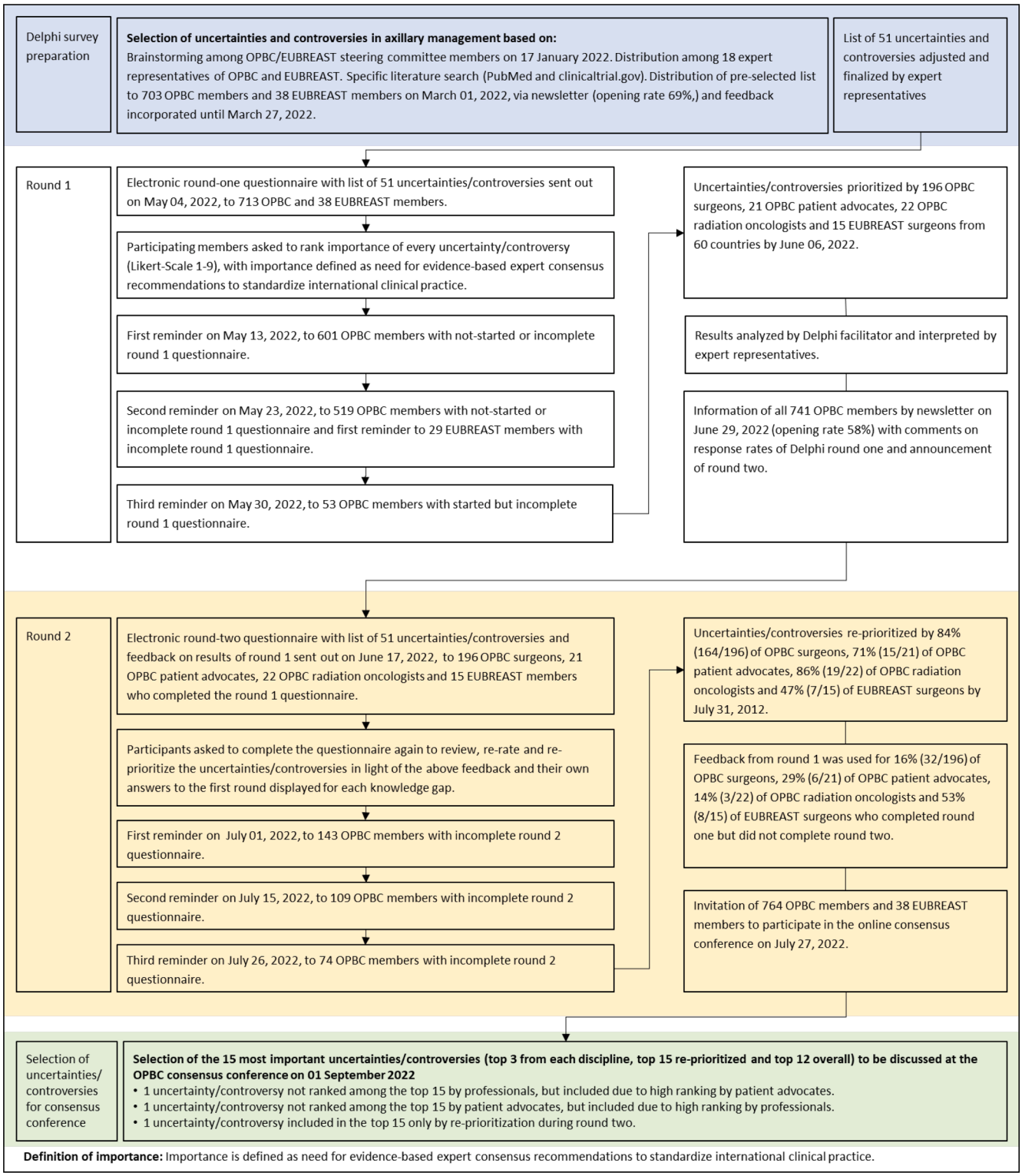

Fig. 1. The Delphi process.

representatives (MH, NM) to identify questions particularly relevant to routine clinical practice. In order to determine whether an uncertainty or controversy had already been adequately addressed in the literature, the two expert representatives performed a specific PubMed search on 27th March 2022. They also searched ClinicalTrials.gov on 27th March 2022 to interrogate ongoing clinical trials with a similar aim. The following selection criteria were specifically used for a literature search over the past 15 years (2007–2022): ("inconclusive"[tiab] OR "unknown"[tiab] OR "further research"[tiab] OR "research need"[tiab] OR "gap"[tiab] OR "priority"[tiab] OR "unmet"[tiab]) AND ("breast neoplasm") AND ("axillary surgery" OR "axillary lymph node dissection" OR ("Sentinel Lymph Node Biopsy"[Mesh]) OR "targeted axillary dissection" OR "tailored axillary surgery") OR ("Axillary Radiotherapy" OR "Axillary Irradiation" OR "Axillary Radiation"): Results 161 papers (MEDLINE).

Furthermore, a sub-specified literature search for imaging-based staging between 2017 and 2022 used the following search strategy: ((("Axilla/diagnostic imaging"[Mesh]) AND "Ultrasonography"[Mesh]) AND "Breast Neoplasms/diagnostic imaging"[Mesh]) AND "Lymph Nodes/diagnostic imaging"[Mesh]): Results 20 papers (MEDLINE).

The website ClinicalTrials.gov was searched using the following terms: ("Breast cancer" AND "Axillary lymph node" AND (("Interventional studies" AND ("Phase 3" OR "Phase 4" OR "Not Applicable")) OR "Observational studies" OR "Observational, Patient Registry Studies") AND ("Recruiting" OR "Not yet recruiting" OR "Active, not recruiting"): Results: 112 interventional clinical trials; 37 observational studies; 12 patient registry studies.

To maximize identification of relevant studies, reference lists of screened studies were manually checked and the 'similar articles' feature of the database was also employed for this purpose. Articles were also identified through searches of authors' personal files. The final reference list was generated based on originality and relevance of contents to this work.

Delphi process

Prioritization of uncertainties and controversies was performed according to the pre-specified Delphi process (see Fig. 1).

The Delphi process was coordinated by a trained facilitator from the Department of Clinical Research at the University Hospital of Basel (RS). This included two rounds of surveys that assessed the relative importance of uncertainties and controversies with feed-back of results being anonymized. Importance was defined as need for evidence-based expert consensus recommendations to standardize international clinical practice.

On 01 March 2022, a total of 703 members were included in the distribution of the pre-selected list of questions (Fig. 1). Throughout the Delphi process, the number of registered OPBC members slowly and steadily increased at normal rates.

For Delphi round 1, personalized access links to the electronic round 1 questionnaire were sent out to all OPBC members and EUBREAST-network participants. They were asked to rate the importance of every knowledge gap on a Likert scale from 1 (not important) to 9 (extremely important) within 2.5 weeks after receipt (see supplementary appendix 2A) and two reminders were sent during this time period. The questionnaire was sent to all patient advocates with comprehensive explanations and a glossary for laypersons. First-round non-responders were considered to have declined study participation and were not contacted for the second round.

For Delphi round 2, all participants of round 1 were sent a second personalized access link to the electronic round 2 questionnaire. The round 2 questionnaire consisted of the same list of uncertainties and controversies as in round 1. In addition, the median rating of round 1 was indicated separately for medical professionals and patient advocates (see supplementary appendix 2B). Participants were asked to complete the questionnaire again within two weeks to reprioritize the respective uncertainties and controversies. A total of two reminders were sent during that time. The completed round 1 questionnaire was used for those participants who completed round 1 but did not complete round 2.

Ranking of uncertainties and controversies

Final ranking of importance was determined by averaged inter-group rankings, giving more weight to individual votes in groups with fewer participants. For each group – surgeons, radiation oncologists and patient advocates – ranking was calculated by median Likert rating of each question. In case of equal median Likert rating, the mean Likert rating was used as secondary ranking factor. Thereafter, the overall average median and overall average mean of the three groups was calculated. Ranking was then determined by descending overall average median and overall average mean ratings. Delphi results were computed by ratings from round 2; in case of non-participation in round 2, they were substituted with ratings from round 1.

Consensus conference

An expert panel met online to discuss the 15 most important questions on 01 September 2022 (see supplementary appendix 3A and 3B). In a second virtual room, a group of breast surgeons from the OPBC membership attended the meeting and participated in voting. The 15 most important questions included the top 3 ranked questions from each discipline (patient advocates, radiation oncologists and surgeons) and as many of the overall highest ranked questions until the number of 15 was reached (n = 12, Table 1). The panel and members first voted on which uncertainties and controversies should be addressed directly by clinical practice guideline development projects based on evidence that is either already published or expected from ongoing studies (see supplementary appendix 4A) [14,16,21]. Repeat voting was encouraged in order to seek consensus after discussion. The underlying principle was that due to limited resources, initiation of further research should only be recommended when the panel considered published or ongoing research insufficient to address the given uncertainty and controversy. In this case, a second voting process, aimed to identify the most appropriate study design was undertaken (see supplementary appendix 4B). For this purpose, a research question, which addressed the uncertainty/controversy at least in part, was developed by the expert representatives in PICO (population, intervention, comparison, outcome of interest) format together with a specific proposal for a trial design [33]. Both the PICO research question and the proposed trial design were adjusted according to panel discussions during the conference. Voting followed thereafter if panellists and members considered them appropriate to address the uncertainty and/or controversy. Appropriateness was assessed based on methodological quality (level of evidence), feasibility and applicability of results to the given uncertainty and/or controversy. A simple majority was defined by agreement among 51–75 % of the panellists and consensus by agreement above 75 %.

Findings

Initial brainstorming during the virtual OPBC/EUBREAST- network steering committee meeting on 17 January 2022, complemented by input from 18 expert representatives via email revealed 32 uncertainties and controversies in axillary management (Fig. 1). Based on a specific literature search, expert representatives added six more questions to the list. After the list was sent to all 713 OPBC and 38 EUBREAST-network members for review, another 13 uncertainties and controversies were added, with a final total of 51.

A total of 254 OPBC/EUBREAST-network members from 60 countries ranked the importance of the identified uncertainties and controversies in Delphi round 1 (response rate 51 %): 22 radiation oncologists, 21 patient advocates and 211 breast surgeons (see supplementary appendix 5A and 5B). A total of 205 (81 %) members completed round 2:

Table 1
Final ranking of uncertainties and controversies prioritized during the Delphi process.

Question	Ranking×	Average Median Likert Rating	Average Mean Likert Rating
(Q1) 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?	1	8.33	7.84
(Q25) 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?	2	8.00	7.80
(Q51) What are the clinically most relevant endpoints in axillary management (survival, recurrence, lymphedema, morbidity, patient-reported outcomes)?	3	8.00	7.68
(Q38) In what situations can axillary radiotherapy be de-escalated?	4	8.00	7.66
(Q10) Should we offer patients a choice between observation (Z0011), axillary radiation (AMAROS) and ALND, or should we 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?	5	8.00	7.45
(Q19) 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?	6	8.00	7.31
(Q26) 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)?	7	7.67	7.30
(Q47) What is the best technique for pathology assessment of the SLN and should it be standardized?	8	7.67	7.17
(Q20) 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?	9	7.67	7.07
(Q2) Should there be development of baseline standards for axillary imaging (e.g., similar to false-negative rates for the SLN-procedure)?	10	7.33	7.33
(Q22) 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)?	11	7.33	7.28
(Q29) 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)?	12	7.33	7.20
(Q31) What is standard of care for suspicious findings in internal mammary or supraclavicular lymph nodes on imaging?	13	7.33	7.13
(Q24) Should measures to decrease the false-negative rate of the SLN procedure in initially cN+converting to ycN0 be standard of care, such as use of dual tracer or removal of a minimum of 3 negative SLNs?	14	7.33	7.11
(Q23) 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?□	15	7.33	7.08
(Q9) Should the ACOSOG Z0011 protocol be considered standard of care around the world?±	16	7.33	6.89
(Q34) 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 extended regional nodal irradiation (e.g., levels 1–4, levels 3–4, internal mammary nodes, and combinations)?	17	7.33	6.83
(Q45) What is the best method to mark the sampled node and the best imaging modality to localize it?	18	7.33	6.71
(Q12) What is the role of imaging-guided localization and selective removal of non-palpable biopsy-positive or suspicious nodes in the upfront surgery setting?	19	7.00	7.04
(Q11) What is standard care for non-palpable ultrasound-detected lymph node metastases in a Z0011-eligible patient?	20	7.00	6.83
(Q36) What are the side effects of axillary radiation using modern techniques?*	21	7.00	6.83
(Q30) 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?	22	7.00	6.81
(Q17) Should invasive lobular breast cancer be managed in the same way as invasive ductal carcinoma regarding omission of ALND?	23	7.00	6.76
(Q35) 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)?	24	7.00	6.74

(*continued on next page*)

Table 1 (*continued*)

Question	Ranking[×]	Average Median Likert Rating	Average Mean Likert Rating
(Q16) Should tumor biology have an impact on eligibility of the Z0011 protocol?	25	7.00	6.68
(Q7) What is the role of axillary surgery in ipsilateral in-breast recurrence after previous breast-conserving surgery and SLN procedure?	26	7.00	6.60
(Q33) What is the best nodal irradiation technique?	27	7.00	6.56
(Q28) How many suspicious nodes on imaging should be marked (e.g., clipped) in a patient undergoing neoadjuvant chemotherapy (NACT)?	28	7.00	6.55
(Q42) Should level II be included in standard ALND?	29	7.00	6.47
(Q46) Should the biopsied lymph node be marked (e.g., clipped) immediately or after histologic confirmation of metastasis?	30	7.00	6.47
(Q37) What is the risk of lymphedema in a patient who develops recurrence in the axilla after radiation of the axilla and undergoes ALND?	31	6.67	6.72
(Q21) 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?	32	6.67	6.45
(Q40) How can we prevent axillary web syndrome?	33	6.67	6.44
(Q5) 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?	34	6.67	6.42
(Q44) What is the best tracer to mark sentinel nodes and when should we use dual tracer?	35	6.67	6.38
(Q13) 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)?	36	6.67	6.29
(Q48) Is there a role for nomograms that predict the likelihood of nodal metastases based on patient, tumor and treatment variables in contemporary axillary management?	37	6.67	6.28
(Q4) Is there an optimal age, size or frailty threshold to omit the SLN procedure?	38	6.67	6.17
(Q14) Should we apply the Z0011 protocol to cN- patients with microscopic extranodal extension in SLN metastases?	39	6.67	6.00
(Q32) What is the best axillary surgery procedure after neoadjuvant radiation therapy?	40	6.33	6.41
(Q8) What is standard of 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?	41	6.33	6.40
(Q3) 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]?	42	6.33	6.18
(Q15) Should the ratio of positive to negative SLNs have an impact on eligibility of the Z0011 protocol (e.g., 2 of 2 versus 2 of 5 removed SLNs are positive)?	43	6.33	6.16
(Q39) Should intercostobrachial nerves be preserved during ALND?	44	6.33	6.07
(Q27) 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?	45	6.00	6.24
(Q41) Should lymphatic vessels be preserved during ALND, e.g. by using axillary reverse mapping or stepwise limited ALND?	46	6.00	6.20
(Q49) What is the optimal follow-up interval and imaging modality for patients after axillary surgery?	47	6.00	5.82
(Q18) In which non-Z0011 eligible patients should intraoperative frozen section analysis of the SLN be standard care?	48	6.00	5.68
(Q50) How should we address lack of sensitivity of axillary imaging during follow-up?	49	6.00	5.61
(Q6) Should we evaluate omission of axillary surgery by delaying the SLN procedure after evaluation of breast pathologic complete response during primary surgery?	50	6.00	5.57
(Q43) When should level III be included in ALND?	51	5.67	5.41

SLN Sentinel lymph node.
ALND Axillary lymph node dissection.
ERNI External regional nodal irradiation.
The 15 most important questions that were brought forward to the consensus conference were highlighted in bold font.
[×] Ranking based on importance, which is defined as need for evidence-based expert consensus recommendations to standardize international clinical practice.
[□] **Q23** was re-prioritized to be within 15 most important questions during Delphi round 2, while being ranked number 16 in round 1.
[±] **Q9** ranked top 3 by surgeons and accordingly, added to the 15 most important questions even though only ranked number 16 overall.
[*] **Q36** ranked top 3 by patient advocates and accordingly, added to the 15 most important questions even though only ranked number 21 overall.

19 radiation oncologists, 15 patient advocates and 171 breast surgeons.

Rating of importance was high generally for most questions, thus confirming that the selection process identified the most relevant uncertainties and controversies in axillary management, with only modest variation among patient advocates, radiation oncologists and breast surgeons, and between round 1 and 2 (see supplementary appendices 6A-B and 7–10). The final ranking of uncertainties and controversies prioritized during the Delphi process is displayed in Table 1. Of these, the 15 most important questions were selected according to the pre-specified selection criteria and included 12 of the 15 highest ranked questions overall (marked with bold font in Table 1). Question 23 was

re-prioritized to be within the 15 most important questions during Delphi round 2. Question 9 was ranked in the top 3 by surgeons and accordingly, was added to the 15 most important questions despite being ranked number 16 overall. Finally, question 36 was ranked in the top 3 by patient advocates and accordingly, was added to the 15 most important questions despite a meager ranking overall (number 21).

The 15 most important uncertainties and controversies were brought forward to the virtual consensus conference. The OPBC/EUBREAST-NETWORK 2022 expert panel consisted of nine patient advocates, ten radiation oncologists, and 39 breast surgeons from 20 countries (see supplementary appendices 3A and 3B). The expert panel attended the virtual consensus conference on 01 September 2022 together with a second group of 70 breast surgeons and radiation oncologists from 31 countries who attended as voting members. All voting results are displayed in supplementary appendix 12. The panel strongly agreed that in general, no further research should be initiated for nine of the 15 most important questions, taking account of studies either already completed or ongoing together with limited resources in the current economic climate (see Table 2 and supplementary appendix 11). The panel reached consensus for recommendation of specific study designs for four of the remaining six questions (see Table 3). For one question, a narrow majority recommendation was reached and for the final question, an appropriate study design could not be agreed on.

Discussion

When this project was planned, it was expected that just a small number of important uncertainties and controversies existed that were amenable to investigation by RCTs. However, patient advocates and the multidisciplinary panel of locoregional breast cancer experts and members of the OPBC and EUBREAST- network identified a relatively large number of open questions of clinical importance that remain unanswered at the present time. Interestingly, systematic evaluation of the 15 most important questions revealed that for nine of these, heterogeneity in routine clinical practice seems to be attributable to an element of disagreement among stakeholders rather than by lack of evidence from previous or ongoing clinical research (Table 2).

Areas for clinical practice guideline development: Standardization of axillary imaging

The first two questions, for which no further prioritization of clinical research was deemed necessary, related to standardization of type and timing of axillary imaging in the context of either upfront (primary) surgery or primary systemic therapy for early stage breast cancer patients. (Q1, Q2) Ultrasound-based staging of the axilla is an operator-dependent technique, reflected in the variable sensitivity (26–94 %) and specificity (53–98 %) of ultrasound [34]. Performance of ultrasound is especially limited for exclusion of low-volume metastatic disease and predicting pathologic complete response in the neoadjuvant setting [6,32,34–36]. Similar performance characteristics are reported for PET CT and MRI, although existing data is more limited [37]. Although publications to date suggest that axillary imaging has several limitations, a large majority of panelists and members concurred that available data are sufficiently robust to be formulated into clinical guideline development by, for example, the “Toolbox” effort [21].

Omission of ALND in node-positive breast cancer

The next set of questions considered to be appropriate for guideline development rather than initiation of further research projects related to omission of ALND in node-positive breast cancer. For clinically node-negative patients with SLN biopsy positive breast cancer, the question of whether the ACOSOG Z0011 protocol should be considered standard of care around the world was rated rather low by both radiation oncologists and patient advocates. However, this question was included in

Table 2
Priorities for clinical practice guideline development selected from the 15 most important uncertainties and controversies in axillary management by the OPBC and EUBREAST panel during the consensus conference.

Uncertainty or controversy in axillary management	No. of votes	Yes	No	Abstain	Final recommendation*
Q1: 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?	55	38	15	2	69 % (Majority)
Q2: Should there be development of baseline standards for axillary imaging (e.g., similar to false-negative rates for SLN procedure)?	62	48	12	2	77 % (Consensus)
Q9: Should the ACOSOG Z0011 protocol considered to be standard care around the world?	58	42	14	2	72 % (Majority)
Q20: 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?	61	49	11	1	80 % (Consensus)
Q22: 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)?	59	44	12	3	75 % (Majority)
Q25: 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?	61	54	7	0	89 % (Consensus)
Q26: 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)?	61	50	9	2	82 % (Consensus)
Q36: What are the side effects of axillary radiation using modern techniques?	60	45	13	2	75 % (Consensus)
Q47: What is the best pathology assessment of the SLN and should it be standardized?	54	36	12	6	67 % (Majority)

* Recommendation to add this uncertainty or controversy to the OPBC agenda for clinical practice guideline development. Majority is defined by agreement among 51–75 % of the panelists and consensus by agreement above 75 %.

‡ As pre-specified in the protocol, discussion and re-voting were encouraged in case of initial majority voting.
SLN: Sentinel lymph node.

the top 15 because it was ranked as the third most important by the breast surgeons (Q9, supplementary appendix 6). Although the panel acknowledged several methodological limitations of the ACOSOG Z0011 study, the observed low rate of axillary recurrence during long-term follow-up (likewise confirmed in the IBCSG 23-01 trial) support omission of ALND in trial eligible patient populations around the world [38,39]. The panel asserted that a more prominent uncertainty relates to selection of patients who should undergo axillary radiotherapy when ALND is omitted. It was acknowledged that conflicting trends exist with de-escalation of axillary surgery on the one hand and broadened indications for extended regional lymph node irradiation on the other. The panel discussed evidence for and against use of axillary radiotherapy in these patients without commenting on the need for further research that is arguably justified in light of available evidence and several ongoing Z0011 validation studies with extended eligibility criteria [5,7–9,40–42].

Similarly, in patients presenting with clinically node-positive breast cancer, the panel failed to make a recommendation to prioritize further research to evaluate the safety of omitting ALND in this patient group. Two ongoing RCTs, one prospective interventional study and one prospective registry to evaluate if ALND can be omitted in patients with residual nodal disease after PST were considered sufficient considering the scarce financial resources for surgical studies. [12,13,19,43–45]. However, the only way to omit ALND in patients with clinically node-positive breast cancer to date is to perform PST and determine nodal pCR with limited axillary surgery. Four prospective trials have demonstrated that the false negative rate (FNR) for SLN biospy in this setting exceeds 10 % [26,30,46,47]. Employing dual tracer mapping, removal of ≥3 SLNs and clipping of any biopsied node have been shown to reduce the FNR to below 10 % [48]. Since all patients in these trials underwent ALND, no data was available on the oncological safety of omitting ALND. Marking the sampled node with a radioactive seed and selective removal without SLN biopsy, a procedure called MARI, reduced the FNR to 7 % and showed low rates of axillary recurrence [49,50]. The combination of SLN biopsy with imaging-guided localization and removal of the biopsied node (known as targeted axillary dissection or TAD), can reduce the FNR to under 4 %. Whether this reduction in FNR achieved with TAD translates into a significant reduction in the rate of axillary recurrence compared to SLN biopsy alone remains unknown. Several multicenter studies, such as AXSANA (EUBREAST-03) and MINIMAX, are currently evaluating the optimal staging technique and long term outcomes after omission of ALND in this population [45,51]. Pre-planned substudies will additionally address the question of whether choice of axillary procedure (SLN biopsy or TAD) should be dependent on the initial clinical tumor size and nodal stage [45,51–54]. The panel was of the opinion that sufficient evidence on regional recurrence rates will be forthcoming in the near future.

Finally, the panel acknowledged that in the context of upfront

Table 3
Research priorities selected by the OPBC and EUBREAST panel from the 15 most important uncertainties and controversies during the consensus conference with recommended research question and study design.

Uncertainty or controversy	Research question in PICO format	Study Design	No. of votes	Yes	No	Abstain	Final voting
Q10b: 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?	P: Patients with clinically node-negative sentinel node-positive breast cancer I: Patient preference-guided treatment C: Physician recommendation O: Patient satisfaction	Randomized controlled trial (cluster randomization by centers with versus without patient decision aid)	62	30	28	4	48 % (No consensus)
Q19b: 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?	P: Patients with residual suspicious findings on imaging after axillary surgery I: observe C: resect or irradiate O: regional/axillary recurrence rate	Register on «forgotten nodes», prospective and/or retrospective	62	38	22	2	61 % (Majority)
Q23b: 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?	P: Patients with confirmed nodal disease at diagnosis (cN+), receiving neoadjuvant chemotherapy I: ycN status based on palpation alone C: ycN status based on palpation and imaging O: proportion ypN + of ycN0, and ypN0 of ycN+	Substudy in AXSANA (prospective register study)	56	48	5	3	86 % (Consensus)
Q29b: 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)?	P: Patients with confirmed nodal disease after NACT (ypN+)I: axillary radiation (or observation for low volume) C: ALND O: Disease-free survival	Pre-specified exploratory subgroup analysis of an RCT comparing axillary radiation with ALND after NACT (TAXIS)	55	48	6	1	87 % (Consensus)
Q38b: In what situations can axillary radiotherapy be de-escalated?	Not applicable	Systematic review and meta-analysis to identify knowledge gaps Delphi process to prioritizeConsensus conference to agree on design of clinical trials (focus on details on radiation trial)	55	47	6	2	85 % (Consensus)
Q51b: What are the clinically most relevant endpoints in axillary management (survival, recurrence, lymphedema, morbidity, patient-reported outcomes)?	Not applicable	Systematic review (meta-analysis), a Delphi process including patients, and a consensus conference with patients and surgeons	50	47	2	1	94 % (Consensus)

surgery, multiple observational studies have consistently shown that ALND should no longer be considered as standard care in all patients with imaging-detected non-palpable nodal disease - almost half this group of patients qualify for the ACOSOG Z0011 protocol [55–57]. Moreover, several authors have also questioned the justification for ALND in patients with palpable nodal disease undergoing primary surgical management. [58,59]. This exact question is being addressed in the OPBC-03/TAXIS trial, in which almost half of patients have palpable nodal disease amongst whom two-thirds undergo upfront surgery [12]. Following intensive discussion and several rounds of voting, a large majority of the panel voted against further prioritization of this aspect of axillary de-escalation in view of several planned RCTs investigating the safety of ALND omission for clinically node-positive breast cancer in the adjuvant setting. The "Toolbox" group was tasked to develop clinical practice recommendations that can be applied until these results become available [21].

Contemporary morbidity of modern axillary surgery and radiotherapy techniques

The panel was adamant that preoperative patient information must include appropriate risk estimates that are based on data available in the literature. Although data on arm morbidity were not available from the randomized ACOSOG Z0011 and IBCSG23-01 trials, the AMAROS and OTOASOR trials published reported clinical signs of lymphoedema as an outcome measure one year after surgery. Rates of lymphoedema were 28 % and 15.3 % in the ALND group compared with 15 % and 4.7 % in the SLN biopsy (plus axillary radiotherapy group) for these two trials, respectively [60]. No differences in patient-reported quality of life (QoL) were reported but it should be noted that *patient-reported* symptoms of lymphoedema are more likely associated with QoL than *objectively* measured lymphoedema [61]. Nonetheless, a recent report from the randomized SENOMAC trial confirmed existence of significant differences between SLN biopsy and ALND and SLN biopsy alone in terms of patient-reported outcomes, but not in self-reported QoL [8]. The ALMANAC trial found a much greater proportion of self-reported sensory deficit in the ALND compared with SLN biopsy groups (31 % versus 11 %, respectively). Finally, the randomized NSABP B-32 trial reported significant differences in a range of upper limb morbidities including shoulder abduction, numbness and arm tingling [62].

Data on comparison of SLN biopsy versus no axillary surgery remain scarce. The randomized INSEMA trial showed statistically significant differences in patient-experienced arm symptoms favoring the group without any axillary surgery [31]. In the SOUND trial, arm and shoulder symptoms increased significantly more rapidly in the SLN biopsy group than in the observation only group one week after surgery [6]. Definitive results covering a longer follow-up period are eagerly awaited.

The question on adverse side-effects of axillary irradiation using modern techniques was rated as very important by patient advocates, despite not being prioritized by radiation oncologists. This indicates that radiotherapy side effects have been a major issue for patients, but may be underreported in the scientific literature [63,64]. Radiation oncologists attribute this to varying radiotherapy (planning) techniques and many point out that documented side effects from historic series have no relevance to contemporary planning methods and modern radiotherapy techniques (including target volume delineation) [65]. The panel therefore reached a majority decision to focus less on collecting additional evidence, but strongly encouraged efforts to consolidate expert consensus recommendations aimed at standardizing international practice, and facilitating continuing education on this key issue affecting routine clinical work.

Standardization of pathology assessment of SLN

International, national, and center-specific guidelines for assessment of SLNs in breast cancer patients exist [66–68]. Whereas most centers standardize pathological examination within a cognate laboratory, there is considerable variation among European institutions [69]. Commonly, deep(er) sectioning of tissue and use of immunohistochemistry is limited to clinical scenarios where micrometastases or even isolated tumor cells (ITCs) may have an impact on patient treatment and outcomes: these include the lobular phenotype and/or analysis of lymph node tissue after PST [67]. Within clinical trials, methods for assessment of lymph nodes must be prespecified and clearly stated as trial outcomes may be dependent on the nuances of histopathological examination.

Areas for further research

There were five of the 15 most important uncertainties and controversies where the panel considered completed or ongoing research to be insufficient and recommended specific studies (Table 3). The first example was a majority recommendation for a registry study on "forgotten nodes" that could be retro- or prospective or a combination thereof [70]. The registry should collect information on axillary treatment of those patients with suspicious residual findings on imaging conducted after axillary surgery. This scenario is expected to be more frequent as a consequence of extreme surgical de-escalation. The panel further recommended clarifying the definition of a complete nodal response (ycN0); this in turn permits limited axillary surgery (i.e., SLN biopsy or TAD) with the aim of omitting ALND. The panel discussed the potential role of ultrasound in this setting but emphasized its limitations when used prior to upfront surgery. It was also noted that clinical complete nodal response is not clearly defined in some ongoing trials, such as NSABP-B-51 [55–57,71]. A consensus recommendation was to conduct a sub-project within the AXSANA trial and this was agreed by the coordinating investigators as EUBREAST- network panellists (TK, JdB, OG) [45]. The third consensus recommendation related to a prospective subgroup analysis to assess the maximum residual tumor load in the axilla after PST that can be adequately controlled by axillary radiation instead of ALND. Two ongoing prospective trials with a focus on low-volume disease are either not randomized or have already completed accrual. The panel therefore favored an amendment to the OPBC-03/TAXIS trial protocol (this trial had accrued 637 of 1500 patients by December 2022) [12,13,19,43,44].

There was much uncertainty about what should be the most appropriate endpoints in axillary management and the panel identified this as an important area for further investigation. There was a high level of consensus (94 %) that this should be addressed with a systematic review and meta-analysis, followed by a Delphi process and a consensus conference with both patient advocates and surgeons as participants. Finally, the panel acknowledged the need for further research on shared decision-making and discussed whether patients with clinically node-negative, SLN biopsy positive breast cancer should be offered the choice between observation, axillary radiotherapy or ALND. There was failure to agree after prolonged discussion on a proposal for a randomized controlled trial with cluster randomization by centers (with versus without patient decision-aid) in PICO format.

De-escalation of axillary radiotherapy

De-escalation of radiotherapy was identified as another area demanding further research. This might permit omission of regional nodal irradiation, or irradiation of only a limited number of levels based on risk of involvement [72]. It should be discussed in terms of sequencing surgery and systemic therapy (i.e., upfront surgery vs. surgery after systemic therapy), type of axillary surgery (e.g., ALND, SLN biopsy, TAD), and risk of nodal involvement (e.g, nodal staging, and other risk factors). In the context of upfront surgery, there are several prospective trials that provide high-level evidence to guide clinical practice [73]. When surgery follows PST, evidence supporting de-escalation or omission of radiotherapy is less straightforward. The prospective cohort study RAPCHEM (BOOG 2010–03) evaluated de-

escalation of nodal radiation volumes in cT1–2 N1 breast cancers stratified into three risk groups. Dose of radiotherapy was based on tumor response to PST and the trial has shown promising results. Moreover, several other trials are evaluating de-escalation of loco-regional therapy according to response to PST [74]. Consequently, the panel strongly recommended a systematic review of the literature followed by use of Delphi and consensus methods by an international and interdisciplinary panel of experts and patient advocates. This panel's remit would be to design a clinical trial exploring the feasibility of strategies to de-escalate axillary radiotherapy.

Limitations

This type of work does not generate, analyze, interpret or report clinical patient data per se. Instead, its primary aim is to identify and prioritize knowledge gaps and evaluate the most appropriate ways to address them by systematically juxtaposing published and ongoing studies in the context of expert and patient opinion. In addition, there was a considerable imbalance between the number of patient advocates, radiation oncologists and surgeons. This may have affected the rankings and it's possible that with a different balance of specialties in the room, a different ranking would have been reached. During the Delphi process, the voice of the patient advocates and radiation oncologists were balanced with the voice of the surgeons by use of averaged inter-group rankings to make sure that the ranking reflects the priorities of all three groups. This was considered necessary because the ratio of surgeons to patient advocates and radiation oncologists was close to 1:10. We refrained from applying this methodology to the consensus conference for the following reasons: Firstly, this ratio was much lower (close to 1:4). Secondly, the methods used for the OPBC consensus conferences were largely inspired by the St. Gallen international breast cancer consensus conference [11]. Thirdly, we knew from the Delphi process that the overall rating of importance differed by group much less than the ranking (supplementary appendix 6A). The primary aim of this project was to identify and prioritize knowledge gaps that would serve as basis for the development of the research agenda and clinical practice guidelines of the OPBC as a loco-regional group. The next steps for the actual development of these guidelines and projects will encompass a broad multidisciplinary approach with panelist expertise in breast imaging, medical oncology, clinical epidemiology and biostatistics and representation from research support units as well as surgical trainees. Finally, the majority of panelists were from Europe, which reflects the composition of OPBC membership. However, discussion and perspective were rather global, since 12 of the 58 panelists (20.7 %) came from outside Europe (see supplementary appendix 3A). Another 18 non-European breast surgeons participated in online voting and discussion, thereby supporting international applicability of the findings.

Conclusion

More than 250 breast surgeons, patient advocates and radiation oncologists from 60 countries identified 51 important uncertainties and controversies in axillary management. The 2022 OPBC/EUBREAST-network panel agreed that research should no longer be prioritized for standardization of axillary imaging, axillary surgery de-escalation in node-positive breast cancer and risk profiling of modern axillary surgery and radiotherapy. Specific research projects were recommended for management of residual nodal disease in the axilla after surgery and identification of the most relevant endpoints in axillary management. The panel further recommended conducting a systematic review and meta-analysis to identify knowledge gaps in axillary radiotherapy de-escalation, followed by a Delphi process to prioritize and a consensus conference to agree on the design of topical clinical trials. In addition, the panel acknowledged the importance of shared decision-making when selecting among medically appropriate options. Since the identified research priorities are not in the focus of industry, the recommended study designs will support competitive public funding applications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributions

WPW and MG initiated and led the whole process. PD, JS, UGB, JH, FF, ZM, JdB, CT, TK, MBP, RdM, ND, SK, OKP, PP, OG were expert representatives. WPW, NM, MH selected the references from the literature search for this review. All authors except RS, NM, MA, LCL, JL, FS, RE, MH were panelists. All authors contributed substantially to the design of the work, as well as to the acquisition and analysis of data. All authors helped draft the work, revised it critically for important intellectual content, and read and approved the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2023.102556.

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