The Lucerne Toolbox 2 to optimise axillary management for early breast cancer: a multidisciplinary expert consensus

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Summary

Clinical axillary lymph node management in early breast cancer has evolved from being merely an aspect of surgical management and now includes the entire multidisciplinary team. The second edition of the "Lucerne Toolbox", a multidisciplinary consortium of European cancer societies and patient representatives, addresses the challenges of clinical axillary lymph node management, from diagnosis to local therapy of the axilla. Five working packages were developed, following the patients' journey and addressing specific clinical scenarios. Panellists voted on 72 statements, reaching consensus (agreement of 75% or more) in 52.8%, majority (51%–74% agreement) in 43.1%, and no decision in 4.2%. Based on the votes, targeted imaging and standardized pathology of lymph nodes should be a prerequisite to planning local and systemic therapy, axillary lymph node dissection can be replaced by sentinel lymph node biopsy (± targeted approaches) in a majority of scenarios; and positive patient outcomes should be driven by both low recurrence risks and low rates of lymphoedema.

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Keywords: Breast cancer; Axillary management; Patient journey; Consensus

Introduction

In 2021, the first *Lucerne Toolbox* presented consensus recommendations for locoregional therapy after primary systemic therapy (PST) in early breast cancer.[1] In this first publication, the expert panel addressed questions concerning diagnostic procedures, surgical planning, and pathologic assessment, based on the available scientific evidence and clinical expertise. The consensus was formulated into a toolbox to facilitate practical implementation of the recommendations along the routine clinical patient pathway.

Herein, we summarise the second *Lucerne Toolbox* consensus, aiming to achieve evidence-based agreement and provide recommendations on axillary management in early breast cancer. Significant progress has been made in locoregional therapy for early breast cancer over the past decades. Complete axillary lymph node dissection (ALND), as practiced widely since the late 19th century following the Halstedian concept of anatomic and mechanistic sequential tumour spread,[2] has been challenged by advances in early detection, tumour biology, multidisciplinary approaches, and genomics-driven therapy. These advances have led to improvements in locoregional and distant control as well as overall survival,[3] and moreover, have paved the way for the de-escalation of locoregional therapy (radiation and surgery) which aims to decrease treatment-related morbidity and improve quality of life (QoL) without compromising disease-related outcomes.[3–5] The therapeutic role of axillary surgery has thereby been greatly reduced, being currently mainly reserved for diagnostic staging to guide systemic and radiation therapy.

Subsequently, the role of any axillary surgical intervention has been challenged in clinically node-negative scenarios (cN0), leading to attempts to identify specific patient populations in which sentinel lymph node biopsy (SLNB) can be omitted.[6] In parallel, its role in axillary staging in patients with cN + disease with a clinical remission on primary systemic treatment (ycN0) is also being challenged. Existing guidelines for locoregional axillary management with surgery and radiation[7–9] are progressively questioned regarding their relevance in light of highly effective systemic therapies and the improved understanding of tumour biology, leading to wide variations in clinical practice between centres and countries. In addition, the application of averaged outcomes to a specific patient scenario, even those outcomes from high-level prospective clinical studies, leads to uncertainties, very often resulting in more, rather than less, locoregional therapy.

Optimised breast cancer locoregional management requires thorough multidisciplinary understanding of the available diagnostic measures, systemic and locoregional treatment options, and outcomes. We hereby provide the second *Lucerne Toolbox*, to guide axillary breast cancer management, including *out-of-the-box* clinical scenarios, based on the available evidence and expert opinion to ensure excellence in breast cancer care.

Methods

Methodological details concerning expert panel selection, pre-meeting procedures, and measures to ensure financial/intellectual independence have been published.[1] International representation, representation from different international and national societies, and multidisciplinary representation were considered in selecting steering committee and expert panel members. All major European oncology societies delegated one to

two experts. Additionally, for the second *Lucerne Toolbox*, representatives from the Oncoplastic Breast Consortium (OPBC) and the European Breast Cancer Research Association of Surgical Trialists (EUBREAST) were included. Altogether, the expert panel comprised 31 members, amongst whom were patient advocates, surgeons, medical oncologists, gynaecologists, radiation oncologists, radiologists, and pathologists (Supplemental Table S1).

The OPBC, experienced in identifying and prioritizing uncertainties and controversies in breast surgery, held an annual meeting on September 1, 2022, which systematically addressed knowledge gaps pertaining to axillary management.[10] Briefly, the OPBC/EUBREAST consortium prioritized 15 of 51 identified areas of uncertainty/controversy using a modified Delphi process, which included an online literature search and an online conference two weeks prior to the Toolbox consensus meeting. This provided the Toolbox panellists a systematic focus in order to develop statements/questions for consensus voting (Supplemental Table S1) around the identified areas. Importantly, the Toolbox's working packages (WPs) addressed both areas of controversy with sufficient clinical evidence for guideline development and areas of uncertainty with clear unmet medical need that can be solved by achieving broad consensus statements.

The Toolbox steering committee designed five WPs representing each step of the patient's journey related to locoregional therapy, i.e., diagnostics, surgery, pathology, radiation therapy, and outcomes (mainly morbidity and QoL), and provided four clinical scenarios based on anatomic tumour burden in breast and axilla (Table 1). These scenarios were adapted to the type of clinical information that would be available during the patient pathway, e.g., pathologic information in postoperative scenarios and various options including only clinical staging information for decision-making in the case of PST. Table 2 describes the axillary surgical techniques. Supplemental Fig. S1 is a schematic representation of the breast's regional lymphatic drainage.

Case number	Clinical scenario
I	cT1, cN0
IIa	cT1–2, cN1, ≤3 suspicious nodes, upfront surgery
IIb	cN1 undergoing PST
III	cT1–2, cN2[a]
IV	cN3[b]

Abbreviation: PST, Primary systemic therapy. [a]cN2: fixed/matted nodes in levels 1/2 or clearly higher tumour burden expected (e.g., on imaging/palpation or if primary imaging shows more than three nodes). [b]cN3: this scenario includes metastasis to axillary level 3 (infra-) and level 4 (supraclavicular) lymph nodes (cN3a–c).

Table 1: **Clinical scenarios pertaining to the development of statements/questions to be voted upon by the panellists.**

Type of axillary surgery	Description	Clinical setting
Sentinel lymph node biopsy (SLNB)[11]	Identification and removal of the sentinel lymph node(s) marked by a (radioactive) tracer and/or blue dye, and suspicious lymph nodes determined by palpation.	- Upfront surgery - After PST
Targeted approaches[12–14]	Identification and removal of lymph nodes marked with a radioactive seed (i.e., MARI procedure), or identification and removal of marked lymph nodes and SLNB (i.e., RISAS and TAD procedure)	- After PST
Axillary lymph node dissection (ALND)	Resection according to anatomic boundaries of axillary lymphatic basins level I, II. Optional to include level III.	- Upfront surgery - After PST

Abbreviations: PST, Primary systemic therapy; MARI: Marking axillary lymph nodes with radioactive iodine seeds, RISAS: Radioactive iodine seed localization in the axilla with the sentinel node procedure; TAD: Targeted axillary dissection.

Table 2: **Description of the different types of axillary surgery.**

A detailed summary of WP development is provided in the supplement. In summary, we were successful in convening a multidisciplinary expert panel, the selection of topics was based on a prior Delphi process carried out by the OPBC, and all WPs were developed by the expert panel.

Role of funding

Complete funding and organizational support of the consensus meeting was provided by Hirslanden Klinik St. Anna. The funding source had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

A total of 31 panellists participated in the consensus meeting. Consensus voting was carried out using a digital voting system. Two panellists with short-notice cancellations voted via email within a week after the meeting, blinded from the voting results from the meeting. If panellists felt their knowledge or expertise was insufficient for a certain question/statement, they were asked to abstain from voting on that question/statement. Based on the number of votes (yes/no/abstain) on each question/statement, percentages were calculated, with 75% defined as achieving consensus and 51%–74% defined as achieving majority, following similar consensus conferences like the St. Gallen Beast Cancer Conference or the Oncoplastic Breast Consortium.[15,16] The consensus meeting sought to provide guidance on at least two levels—"consensus level" and "toolbox level"—because not all clinical questions have high-level clinical evidence and several solutions/tools may lead to similar outcomes. The essential aim was to simulate real-life challenges in daily clinic. Panellists voted on 72 statements/questions, reaching consensus (agreement of 75% or more) in 52.8% (38 of 72), majority (51%–74% agreement) in 43.1% (31 of 72), and no

decision in 4.2% (3 of 72). Major statements derived from the WPs are summarised in Fig. 1. Clinical treatment algorithms based on the statements are summarised in Fig. 2. Below, we present the voting results for imaging (WP 1), surgery (WP 2), pathology (WP 3), and outcomes (WP 5). Radiation therapy recommendations (WP 4) are listed separately in Table 3. The full list of the questions and voting results are given in Supplemental Table S2.

WP 1: diagnostic requirements to optimise locoregional therapy

Imaging modalities

A majority agreed (70%) that targeted axillary ultrasound should be performed at primary diagnosis, even if suspicious lymph nodes were not noted on the clinical examination or on non-targeted imaging such as diagnostic mammogram/digital breast tomosynthesis (DBT) which only provide limited axillary coverage. Consensus (93.5%) was reached that second-look ultrasound should be used for final decision making in cases of discordance of clinical or radiological exams. In addition, when either clinical or radiological signs of axillary lymph node involvement are present, more than 80% of the panel voted for an additional targeted ultrasound directed to the axilla.

A majority also agreed (56.7%) that axillary ultrasound should comprise B-mode and colour-doppler imaging to improve diagnostic accuracy. Consensus was achieved (93.5%) on which features are associated with high suspicion for malignancy (Supplemental Table S3), which features should be included in the report, and which features should inform the final BI-RADS assessment category.[27–29]

Physical examination alone has a low accuracy to predict nodal involvement.[30] Mammography, DBT, and to a lesser extent also magnetic resonance imaging (MRI) are limited in their field of view (FOV) to evaluate the whole axilla and thereby the full extent of axillary involvement.[27] Imaging modalities used to evaluate systemic disease such as CT, PET/CT, PET/MRI, and single-photon emission computerized tomography/computed tomography (SPECT/CT) are not adequate for axillary staging due to their limited spatial resolution and the variable tracer avidity of different types of tumours (e.g., low avidity in slow-proliferating tumours including invasive lobular carcinoma).[27,31]

In summary, there was consensus that ultrasound remains the gold standard of axillary imaging; perhaps more importantly, ultrasound can be carried out in conjunction with the physical examination and other imaging modalities and can serve as an arbitrament between conflicting imaging results.

Tissue sampling

There was consensus (96.8%) that if a suspicious axillary lymph node is noted on the clinical examination or on imaging, it should be confirmed with targeted axillary ultrasound including percutaneous tissue sampling (fine needle aspiration [FNA] or core needle biopsy [CNB] of the most suspicious node). Importantly, the panellists agreed that sampling of a suspicious node should be performed only if it will have significance for clinical

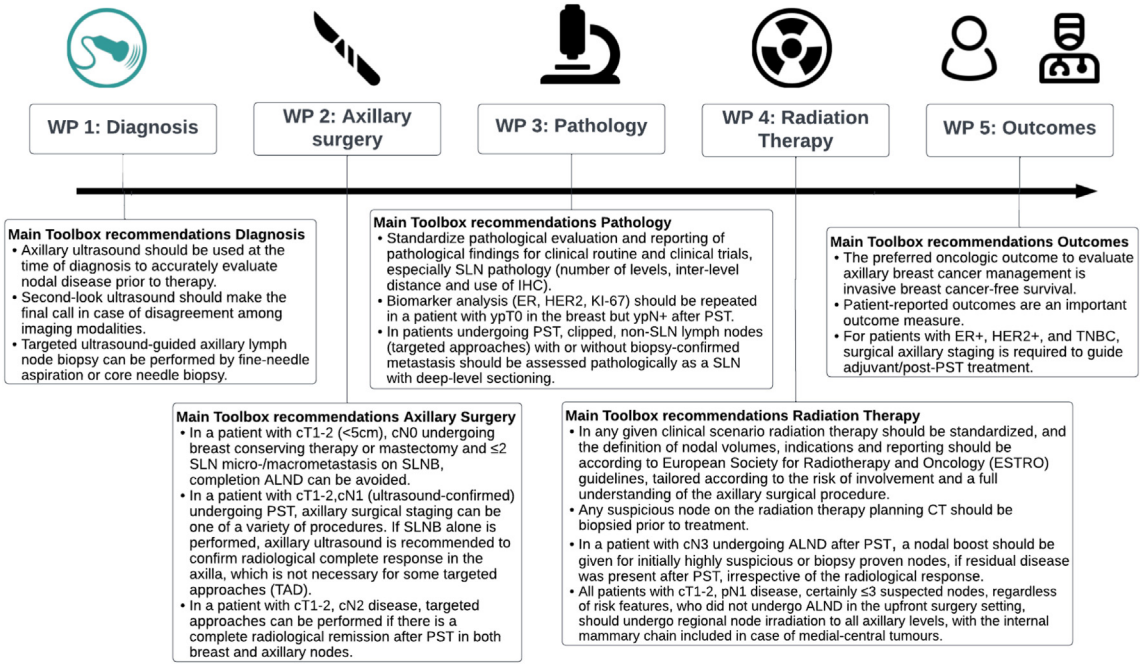

Fig. 1: Main toolbox recommendations for axillary management.

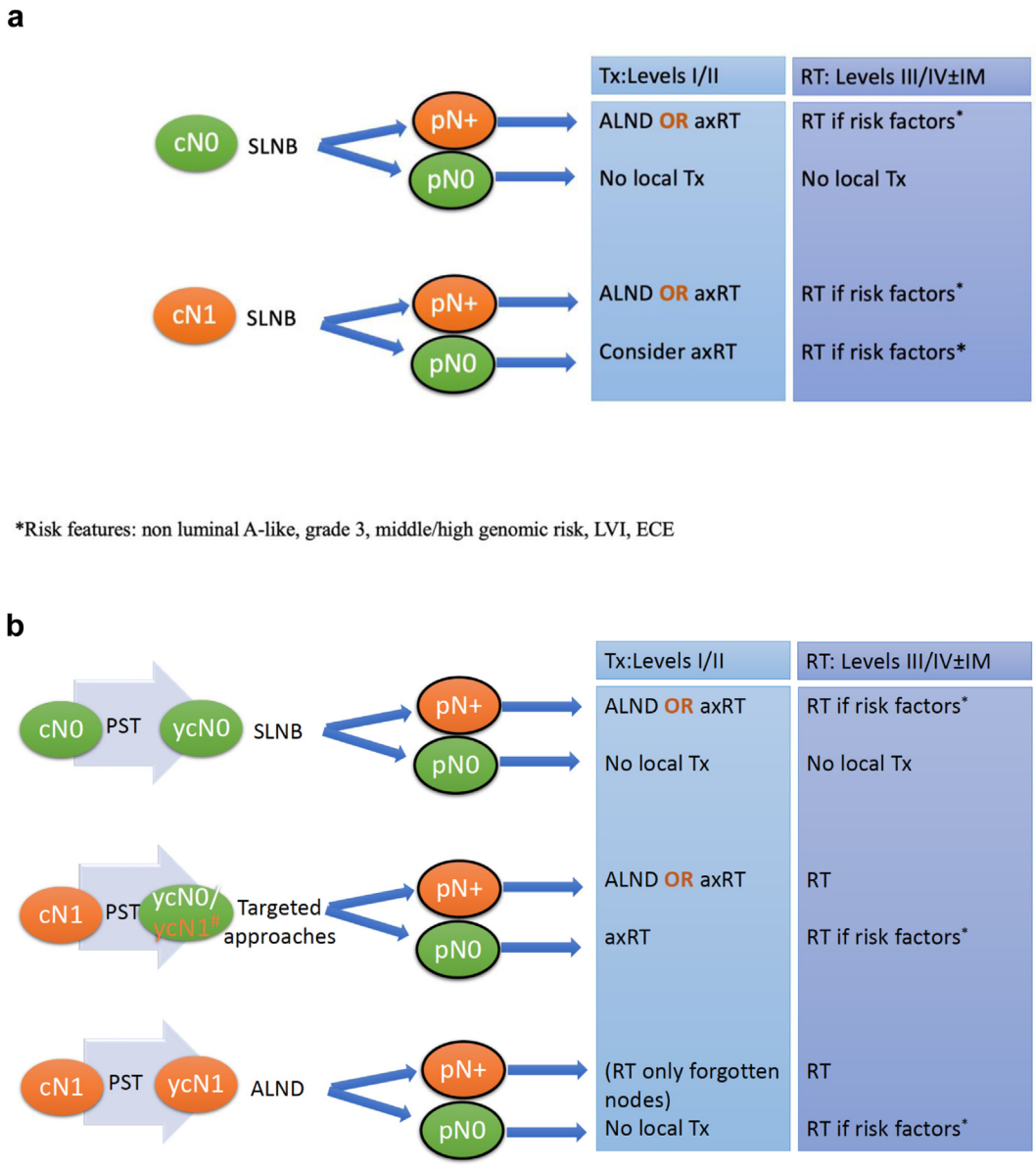

Fig. 2: Treatment algorithms for axillary radiation therapy and surgery. a) Upfront surgery setting. b) Primary systemic treatment setting. Abbreviations: axRT, Axillary radiation therapy; ALND, Axillary lymph node dissection; ECE, Extracapsular extension; IM, Internal mammary; LVI, Lymphovascular invasion; RT, Radiation therapy; SLNB, Sentinel lymph node biopsy; Tx, Treatment.

management (e.g. for patients with HER2 positive disease, a positive node may change the treatment regimen from adjuvant trastuzumab and paclitaxel to primary systemic therapy with dual anti-HER2 blockade). A suspicious node seen on imaging can be biopsied using either FNA or CNB based on institutional or physician preference, as opposed to tissue sampling of the primary breast lesion, where CNB, not FNA, is recommended to allow for full pathological evaluation.[32]

A majority agreed (61.3%) that biopsied lymph nodes should be marked. Importantly, consensus (93.3%) was achieved for the marking of lymph nodes with pathologically confirmed metastasis. Pre-treatment marking of pathologically confirmed metastatic lymph nodes reduces false-negative rates,[12] as shown in ACOSOG Z1071 where there was a reduction of false-negative rates from 12.6% to 4.2%.[33] However, on the preferred type of marking of lymph nodes at the time of diagnosis, there

Topic related to statement	Consensus/recommendation statement	Discussion summary
cT1, cN0	In medial-centrally located breast tumours, the IM and levels 3–4 nodes should *not* be targeted (majority)	The EORTC 22922/10,925 and the MA20 trials included medial-centrally located breast tumours with N0 status due to the risk of IM nodal involvement in these cases.[17] Nowadays, there is better understanding of risk factors and imaging; thus, only in high-risk cases should these volumes be considered for irradiation.
cT1, cN0, omission of SLNB	No agreement on whether SLNB is required to guide RT, especially for the decision whether to include the IM nodes.	Lower regional recurrence rates have been shown in patients with pN0 when treated with whole-breast irradiation compared to intraoperative partial irradiation [1.3% vs. 4.0% ($P < 0.001$)],[18] suggesting the protective effect of an incidental radiation dose to the lower axilla by tangential breast irradiation. An incidental dose within the therapeutic range to the lower axilla in patients treated with breast-only RT was found in 50% of patients, based on the INSEMA (NCT02466737) quality assurance publication.[19] Therefore, in case of omission of SLNB, attention should be paid to the potential benefit of breast RT.
Patients with cT1–2, cN1 disease (non-palpable), who underwent upfront surgery with pN1 (up to 3 nodes)	In case of low-risk features[a] at final pathology, RT volumes should include levels 1–2 and interpectoral nodes (majority). All levels of the axilla (1–4) should be considered for RT according to risk factors; IM nodes should be included in case of medial-central tumours (majority).	Recommendations were based on differences in RT volumes in the ACOSOG Z0011[20] and AMAROS[21] trials, both of which included a relatively low-risk population.
cN1, undergoing PST	cN1, ypN0 For low-risk disease, assume that the incidental dose from tangential breast irradiation to the lower axillary levels is not sufficient (majority). Also, in low-risk disease in the case of TAD or SLNB-only, RT can be applied to the lower axilla (levels 1–2) and to the interpectoral nodes to reduce potential toxicity related to full-axillary RT (majority). For high-risk disease, all levels of regional lymphatics should be irradiated (majority). For medial-centrally located breast tumours in high-risk disease, the IM nodes should be included in the radiation target volumes (majority). pN1, ypN1 If no ALND was performed, all axillary levels, including considering the IM nodes for non-medial-central tumours, should be irradiated (majority).	The radiation oncologist should review the pre-treatment images and surgical/pathology reports to understand the initial and post-PST extent of nodal disease including the levels involved.[22] If possible, the images should be fused to the post-PST radiation therapy planning CT (e.g., pre-PST PET/CT) to assist in delineation (consensus). cN1, ypN0 For cN1 disease involving only lower axillary levels, in the case of ypN0, irradiation of only levels 1–2 and interpectoral nodes can be considered based on the RAPCHEM trial.[5] Meanwhile, for high-risk disease, and/or medial-centrally located breast tumours, all levels of the axilla should be covered, and IM nodes should be included in the radiation target volumes. Patients with high-risk disease will have escalation of systemic therapy and axillary surgery. The pathologic assessment of complete pathology response is limited in its ability. Therefore, it is not advised to de-escalate all modalities, especially as using a delineation atlas and validated constraints for radiation planning reduces potential toxicity.[8] pN1, ypN1 The radiation volume should include all axillary levels 1–4 and IM nodes. See the Taxis trial [NCT03513614].[23] Suspicious nodes on radiation planning CT should be biopsied, and if not amendable for resection, they should receive a radiation boost.[24]
cN2–3, undergoing PST	cN2–3, after ALND, regardless of response Radiation target volumes should include only the un-dissected axilla (majority). ypN0 Nodal boost should be considered only for known involved nodes that are inoperable and suspicious on post-PST imaging (majority). ypN+ Nodal boost should be given for initially highly suspicious or biopsy-proven nodes that were not excised at time of surgery (majority).	In patients with high nodal disease burden after PST, ALND is recommended, and the radiation volumes should include the un-dissected breast lymphatics, based on the EORTC 22922/10,925 trial, aiming to reduce arm morbidity related to combined ALND and radiation.[25] The dissected axilla should be included in the target volumes in case there is suspected residual disease. There are limited data from trials about the use of radiation boost for inoperable disease seen on imaging, but a few reports indicate that it could be applied with relatively low risk for toxicity to improve local control.[26]

Abbreviations: ALND, Axillary lymph node dissection; CT, Computed tomography; ECE, Extracapsular extension; IM, Internal mammary; LVI, Lymphovascular invasion; MARI, Marking the axillary lymph node with radioactive iodine (I) seeds; PET, Positron emission tomography; PST, Primary systemic therapy; RT, Radiation therapy; SLNB, Sentinel lymph node biopsy; TAD, Targeted axillary dissection.
[a]Low-risk features: luminal A-like, grade 1–2, low genomic risk, no LVI, no ECE.

Table 3: **WP 4, radiation therapy statements and summary recommendation.**

was no agreement (see Supplemental Table S2 for the types of marking discussed). Therefore, this should be according to local experience and institutional standards.[34] Consensus was achieved (81.8%) that if targeted axillary surgery is planned after PST, only one involved node needs to be marked prior to PST.

WP 2: optimising axillary surgery

Technique of axillary staging

A majority agreed (68.2%) that a dual tracer in the case of SLNB is not always needed, regardless of whether SLNB is performed before or after chemotherapy. A majority also agreed (59.1%) that the intercostobrachial nerves

should be preserved (if technically feasible) if ALND is performed. Consensus was achieved (100%) that axillary level 3 (infraclavicular nodes) dissection is not needed, unless there is perioperatively palpable or imaging identified disease at that level (Supplemental Fig. S1). Additionally, consensus was achieved (81%) that if ALND is performed, the efferent lymph vessels adjacent to the axillary vein can be identified and preserved.[35]

SLNB in cT1N0 disease

Consensus was achieved (83.9%) that in older patients ≥75 years of age who have comorbidities, who are not candidates for chemotherapy, and who present with low-risk disease defined as unifocal cT1 (a–c) N0 (including axillary ultrasound), SLNB can be omitted, regardless of tumour biology. Nevertheless, a majority agreed (60%) that SLNB-associated morbidity does not justify the omission of SLNB for all patients. Furthermore, a majority agreed (63.3%) that patients usually fully recover from SLNB-associated short-term morbidity (e.g., seroma, pain, restricted range of motion) within one year.

These statements are in line with a number of consensus statements including the 2021 St. Gallen Breast Cancer Consensus, in which SLNB was favoured for most patients in their 80s who are undergoing breast surgery but not for frail older patients because of concerns that any intervention may lead to additional morbidity and that in low-risk disease, SLNB will not provide information to guide therapy.[15] The panel did not discuss omission of targeted axillary ultrasound in low-risk breast cancer.[36]

The IBCSG10-93 study and the study by Chung et al. omitted axillary evaluation in cN0 disease.[37,38] However, HER2/neu-enriched or triple-negative tumours may recur within 2 years and 30% of the older patients with cN0 ER-positive breast cancer will have positive nodes on SLNB.[39,40] Therefore, age alone is not sufficient as a criterion to omit SLNB. Therefore, as SLNB may provide diagnostic information for selecting systemic therapy and radiation therapy,[41] the decision to omit SLNB should be based on proper clinical evaluation, including frailty assessment and comorbidity scales. The "safe omission" of SLNB can be performed in patients with low-risk for nodal disease, such as luminal A disease with a tumour size ≤1 cm (pT1a,b) and axillary ultrasound-confirmed cN0, as the likelihood of pN2–3 disease in older patients with cN0 unifocal disease is low.[42,43]

Several prospective randomized trials are investigating the omission of SLNB in patients with tumours smaller than 2 cm who have a negative axillary ultrasound and planned breast conservation (BOOG trial NCT02271828, INSEMA trial NCT02466737, NAUTILUS trial NCT04303715, and SOUND trial NCT02167490). The SOUND trial (n = 1463) has recently presented data showing the non-inferiority of distant disease-free survival when omitting SLNB in this select group of patients.[44] Interestingly, adjuvant therapies including the use of chemotherapy were comparable in both treatment arms, with data on irradiation volumes not presented.

ALND in SLN positive disease

There was consensus (83.9%) that in the case of cN0 disease together with breast conservation and ≤2 SLN metastases on SLNB, completion ALND can be avoided regardless of tumour biology or age. By contrast, in the case of 3 SLN metastases, consensus was reached that completion ALND should be considered (77.4%). In the case of mastectomy together with ≤2 SLN metastases on SLNB, a slim majority agreed (56.7%) that completion ALND can be avoided regardless of tumour biology or age. These voting results were based on published results from pivotal trials that were conducted in T1–2, cN0 patients with limited nodal burden on SLNB,[45,46] including ACOSOG Z0011 (breast conservation only)[20] and EORTC 10981–22023 AMAROS (T ≤ 3 cm, cN0, breast conservation or mastectomy),[47] which showed no significant differences in the cumulative incidence of axillary recurrence, disease-free survival, and overall survival at 10 years between ALND and SLNB with higher arm morbidity, especially oedema, in the ALND group. As ACOSOG Z0011 only included patients with ≤2 SLN metastases, and only 5% (35 patients) of patients in AMAROS had ≥3 SLN metastases, there is a paucity of prospective data on omitting ALND with a larger nodal tumour burden. It should be kept in mind, however, that radiotherapy in these patients is debated if ALND is omitted as ACOSOG Z0011 seemingly investigated the omission of both ALND and axillary radiotherapy,[20,46,48] while AMAROS investigated the replacement of ALND by axillary radiotherapy[45,47] (see radiotherapy section below).

Axillary staging after primary systemic treatment

Consensus was achieved (82.8%) that in the case of ≤2 suspicious nodes on ultrasound (including those with pathologic confirmation of nodal disease), axillary surgical staging can be one of a variety of procedures including a targeted approach (Table 2).[11–14,49] The role of axillary ultrasound to determine radiologic complete response remains controversial[50]: If SLNB alone is used the role of axillary ultrasound is important in order to maintain a low FNR, whereas in some of the targeted approaches (TAD) full radiological remission is much less important since the method has been shown to deliver low FNR even in patients without full remission. As fewer than one-third of the patients included in the trials evaluating targeted axillary procedures have been those with ≥4 suspicious nodes on initial imaging, the current recommendation for SLNB or targeted approaches includes only patients with ≤3 suspicious nodes on pre-treatment imaging.

Residual nodal disease seen on post-surgery imaging

Consensus was achieved (76.7%) that any suspicious node noted on radiation therapy planning CT should be biopsied prior to radiation, regardless of tumour response to PST or type of axillary surgery (i.e., including in the case of ypN0 and/or ALND). A majority agreed (72.4%) that if such a node is confirmed to be pathologically involved, the preferred approach is surgical excision prior to radiation therapy.

Consensus was achieved (93.1%) that if the initial axillary surgery was SLNB or a targeted approach, the preferred surgical approach is completion ALND prior to radiation. If re-operation is not feasible without exposing the patient to risk of excessive morbidity, consensus was achieved (80%) that a radiation boost to the involved node should be applied.

WP 3: pathologic requirements to optimise locoregional therapy

Standardised protocols

Consensus was achieved (96.8%) that local pathology should have standardised assessment protocols based on standard slices and indications for immunohistochemistry to assess lymph node metastasis. These details should also be clearly defined in clinical trials (96.7%). Notably, the number of slices, number of levels, inter-slice distances, and the use of immunohistochemistry vary widely according to national/local guidelines and between clinical trials.[51] A review of pN0 disease in the NSABP-B32 trial found a 15.9% rate of occult nodal involvement (11.1% with isolated tumour cells, 4.4% with micrometastases, and 0.4% with macrometastases, with upstaging to pN1 in ~5% of the cases).[52] Thus, pathologic methodology must be defined and shared with the multidisciplinary team. The amount of residual nodal disease will dictate the need of completion of axillary dissection and/or additional radiation or systemic therapy.

Vascular invasion and extracapsular extension

There was no agreement (43.4%) on reporting the presence of microscopic vascular invasion in the biopsy specimen of the primary lesion. Venous vascular invasion may not be distinguishable from lympho-vascular origin and presence of vascular invasion should be assessed from the primary tumour biopsy and surgical specimen.[53]

Consensus was achieved (83.9%) that microscopic presence or absence of extracapsular extension (ECE) in positive lymph nodes (SLN and non-SLN) should be reported. While there is no current standardised pathological definition of the extent of ECE and no grading of ECE extension, in some studies, ECE >1 or 2 mm has been regarded as extensive ECE and its presence associated with non-SLN involvement and poor prognosis.[54]

Sentinel vs. non-sentinel lymph node handling

All panellists agreed (100%) that pathologic assessment of SLN in patients undergoing upfront surgery should be directed toward identifying macro- and micrometastasis and a majority agreed (71%) that additional immunohistochemical assessment of lymph nodes is helpful to identify micrometastasis in patients with lobular carcinoma undergoing upfront surgery. Notably, the introduction of new diagnostic techniques might lead to stage migration and misleading statistics regarding breast cancer-specific outcomes[55]; thus, the extent of pathologic evaluation should be clearly reported in both the routine clinical context and in trials for an in-depth understanding of outcomes. The detection of isolated tumour cells does not alter clinical management; therefore, it is our recommendation that the pathology protocol does not include an extensive search for low-volume metastatic nodal disease.

Consensus was achieved (100%) that for patients undergoing upfront surgery, the macroscopic/microscopic observation of a clip/marker in a lymph node should be reported in all cases. For patients undergoing PST, clipped, non-SLNs (e.g., targeted approaches; Table 2) should be assessed pathologically with deep-level sectioning, similar to SLNs (86.7% and 80% agreement for marked non-SLNs with and without biopsy-confirmed confirmed metastasis, respectively). In the context of targeted approaches, both SLN and non-SLN (clipped node) pathologic evaluations are important to detect residual nodal disease which dictates the need for completion ALND and/or additional radiation or systemic therapy. In the post-PST context, minor metastatic nodal deposits are also important to estimate the volume of viable cells to determine the residual cancer burden; therefore, extensive lymph node evaluation in this context is recommended to identify tumour cells including isolated tumour cells. In addition to SLN and non-SLN marked nodes (e.g., with Clip) lymph nodes that appear positive during intraoperative palpation should be removed and treated as SLN during the pathology work up. The majority agreed (60%) that observed fibrosis in an SLN can be considered a reliable indicator of prior macro-metastasis in cN0 patients undergoing PST.

Biomarker analysis after PST

Consensus was achieved (80.6%) that biomarker analysis (ER, HER2, Ki-67) should be repeated in patients with ypT0 in breast and ypN + after PST on the positive node to exclude discordance, as changes in biomarker expression may have significance for further systemic therapy.[56]

WP 4: axillary radiation therapy

Radiation therapy statements and summary of the recommendations are listed in Table 3. Panellists were

familiar with the published literature regarding the role of radiation therapy in treating nodal disease and the caveats of current practices. For example, EORTC 22922/10,925, which was one of the pivotal trials establishing the effect of radiation therapy on the undissected part of the axilla and internal mammary nodes in breast cancer, included three radiation techniques for nodal irradiation.[57,58] The trial was subjected to central radiation quality assurance, and a recent analysis showed that the different techniques had clinically relevant differences for toxicity and disease outcomes.[47] In addition, the panellists highlight that current breast radiation therapy practice mandates a full understanding of the volumes at risk, including information on pre-treatment imaging and the type of surgical procedure, especially in the presence of de-escalation of surgery. Careful delineation of nodal volumes allows understanding the true anatomical limits of axillary surgery and enables the detection of residual suspicious nodes after surgery.[24] The role of nodal boosts after PST was discussed due to limited data in the literature. The recommendations are that in the case of pathologic complete response, a nodal boost should be omitted for initially involved nodes (e.g., known involvement of axillary levels 3/4, internal mammary nodes) that do not appear suspicious on post-PST imaging. Recommended radiation target volume selection and nodal boost indications are summarised in Table 3.

Fig. 3 shows a radiation planning CT of a patient after ALND, in which the surgical procedure included only level 1. Therefore, in this case, the undissected axilla includes axillary levels 2–4 and rotter nodes. This is opposed to 2D-based field-based planning based on a medial supraclavicular field only. Not covering these volumes in a high-risk patient may result in nodal recurrence at the low-dose/no-dose volumes in between the operated and irradiated parts of the axilla.[22]

WP 5: outcomes

Oncologic outcomes

Consensus was achieved (86.7%) that the preferred oncologic outcome to evaluate axillary breast cancer management is invasive breast cancer-free survival. A majority agreed that distant disease-free survival (54.8%) and axillary control (66.7%) are not adequate endpoints to evaluate axillary breast cancer management.[59]

Morbidity and patient-reported outcomes

Among the statements that were related to morbidity and patient-reported outcomes, there was unanimous agreement that selective nodal surgery (e.g., SLNB, targeted approaches; Table 2) causes less morbidity (e.g., seroma, hematoma, lymphedema) and results in better patient-reported outcomes (e.g., pain, dysesthesia, restricted arm movement) compared to ALND. Therefore, these procedures should be offered to eligible patients. Consensus was achieved (96.6%) that short-term morbidity (e.g., seroma, pain, restricted range of movement) of ALND does not fully recover within one year. Consensus was also achieved (e.g., 89.3%) that patient-reported outcomes of locoregional therapies should be collected and reported to guide future approaches. Some attention should be paid to the question of which patient-reported outcomes to collect. Recent patient-reported outcomes for the INSEMA trial

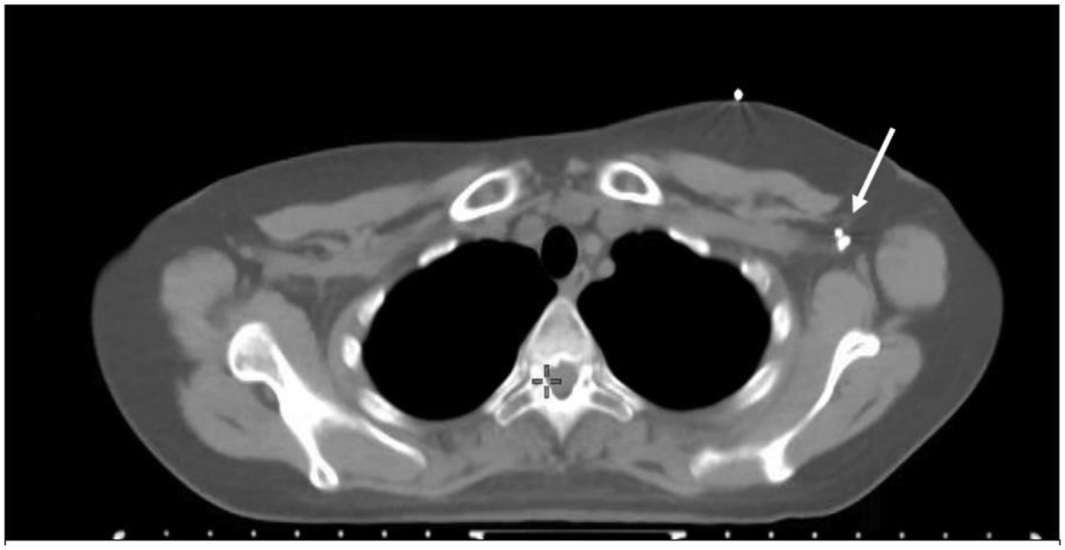

Fig. 3: Radiation planning CT after axillary lymph node dissection. The arrow shows the clips at the upper border of axillary dissection. No surgical changes are noted behind the pectoral minor muscle, suggesting only partial axillary dissection of level 1 without level 2.

demonstrated a clinically meaningful effect of no SLNB vs. SLNB vs. ALND on arm-specific symptoms (including pain, arm swelling, and impaired mobility) but not on overall QoL (QLQ–C30).[60,61]

Discussion

The majority of early breast cancer patients are cured by modern multi-modality treatment which includes locoregional surgery and radiation therapy as well as systemic therapy. The goal of breast surgery is to completely excise the tumour,[62] while the goal of irradiation is to eradicate microscopic residual disease. The rationale and goals of axillary surgery, however, are more nuanced.

A number of prospective randomized trials investigating the omission of ALND in patients with involved sentinel lymph nodes have demonstrated that in up to 39%,[45] residual metastatic lymph nodes remain present. Importantly, no detrimental impact on local recurrence or disease-free survival was seen, while lymphoedema risks were halved.[20,63,64] Given these observations, axillary local management has undergone significant changes in clinical practice, leading to the need for consensus and detailed recommendations.

Preceding the Toolbox consensus meeting, the OPBC and EUBREAST identified and prioritised major uncertainties/controversies in axillary surgery, facilitating our focus on both unmet clinical issues with insufficient evidence as well as controversial clinical issues with sufficient evidence for clinical guideline development.[10] The WPs focused on several clinical scenarios that are relevant for the management of locoregional therapy for breast cancer. The main outcomes and recommendations are summarized in Fig. 1, and the main controversial aspects are put into context in the results section. Beyond the results presented here, two topics in axillary management require further discussion: a) the impact of advances in surgical technique and the contemporary application of radiation treatment volumes on treatment recommendations and b) the possible impact of reduced adjuvant systemic treatments in case of scenarios where fewer lymph nodes are resected and evaluated.

Axillary therapy after PST provides an interesting example of how technical advances drive expert recommendations. Three prospective, non-randomized trials in patients with limited nodal involvement at diagnosis who received PST and SLNB followed by ALND showed highly similar outcomes, including that on average, SLNB alone showed unacceptably high false-negative rates.[33,65,66] Of note, the OPBC did not identify this topic to be of specific additional research interest and in the toolbox consensus, 82.8% voted against ALND performed with advanced surgical techniques (Table 2) and/or additional imaging. Given the lack of sufficiently powered and prospective survival data for this approach, it is likely that experts voted based on prospective surgical data that show the reliability of targeted approaches instead (Table 2).[14,65,67] In this context, long-term survival data for different axillary staging techniques in nodal positive breast cancer patients are highly desired.

In addition to advances in surgical technique, experts recognize that three-dimensional volume-based design of radiation treatment has evolved from historical field-based approaches. In this respect, the EBCTCG meta-analysis showed improved breast cancer outcomes after nodal irradiation in patients with involved axillary nodes.[68] An updated EBCTCG meta-analysis showed strengthened benefits in patients treated in more recent trials, even dating from before contemporary radiation treatment techniques, allowing further reduced doses to the heart and lung.[69] In summary, we observe that experts are willing to optimize, and in many cases, de-escalate axillary therapy with the goal of minimizing lymphoedema even if high-level outcome data are lacking.

The interactions between nodal surgery/radiation treatment and the indications for systemic therapy, including response-dependent systemic therapy after PST, are complex.[70–73] Completion ALND could indicate more intensive adjuvant treatment, including abemaciclib combined with endocrine treatment for high-risk luminal breast cancer, capecitabine for triple-negative breast cancer, or T-DM1 for HER2-positive patients with residual axillary disease after PST.[74] Current guidelines still indicate ALND if $\geq$ 3 SLN are positive; however, some important information may be lost in patients with lower axillary tumour burden. According to the ACOSOG Z0011 trial, almost 14% of patients with 1–2 positive SLNs had $\geq$4 positive nodes after ALND,[20] implicating that we are potentially undertreating a significant fraction of patients eligible for abemaciclib.[72,73] Of note, the above-mentioned trials were medical intervention studies, not surgical trials, and thus were performed after breast and axillary surgical procedures as determined by contemporary practice that have since evolved. Therefore, the toolbox experts' opinion remains that there is no need to perform ALND in most patients, thereby avoiding the morbidity associated with merely seeing if a patient needs additional systemic therapy. However, future research may focus on developing new risk scores for (high) nodal involvement to indicate more intensive adjuvant treatment in times of de-escalated axillary surgical staging. In the PST setting, for example, an intelligent algorithm using only pre-surgical variables recently showed reliable exclusion of residual tumour in the breast and axilla.[75]

The main strengths of this toolbox endeavour include the inclusion of all major European oncologic societies, recognized leaders in the field, representatives from major European study groups and patient advocates. In addition, the collaboration with OPBC[10] allowed a more targeted, standardized and systematic approach of

including controversies that have been identified and prioritized previously by the use of established Delphi methods. However, several recommendations are not fully evidence-based ones. In the case of technical recommendations (e.g., types of axillary surgery, application of irradiation volumes), experts considered a number of "tools" to achieve a technical goal, recognising a lack of evidence concerning several technical innovations. In cases where de-escalation was suggested, the focus was always to allow for a clear improvement in quality of life even if survival data were not fully available. That being said, the recommendations by the panellists are directed toward well-established multidisciplinary teams, typically in breast cancer centres that undergo regular audits and certification procedures. The recommendations are limited not only by the clinical scenario but also require discussion in multidisciplinary team meetings. In addition, the consensus does not address all patient-related factors, breast cancer subtypes, genomics signatures, and other factors that may contribute to the treatment approach. Breast cancer is an intricate disease that mandates a comprehensive understanding and multidisciplinary.

Overall, this Toolbox consensus on axillary therapy in early breast cancer allows for the adaptation of management approaches in specific clinical scenarios based on expert opinion and consensus agreement. The second *Lucerne Toolbox* follows the actual patients' workflow in daily clinical practice to guide its recommendations, emphasizing that only a multidisciplinary approach can ensure excellence of care for the benefit of our patients. The recommendations are likely to be useful across a large spectrum of individual patients, not only for suggesting local therapies, and are of interest for the entire multidisciplinary team.

Search strategy and selection criteria

The second Toolbox consensus collaborated with the OPBC/EUBREAST consortium to systematically identify and prioritize areas of both sufficient evidence and uncertainties in axillary management. Briefly, the OPBC/EUBREAST consortium prioritized 15 of 51 identified areas of controversy/uncertainty by means of a modified Delphi process, which included an online literature search and an online conference two weeks prior to the Toolbox consensus meeting. This provided the Toolbox steering committee a systematic focus to develop statements/questions for consensus voting around the prioritized areas. The scope of the consensus statements/questions was defined based on the actual and complete patient journey from diagnosis to local therapy of the axilla that would enable healthcare professionals to provide a maximum number of valuable local treatment options. Each statement/question was verified in terms of the published scientific evidence using a literature search of PubMed, Embase, Medline, and Google, both before the voting and afterwards during the writing process.

Contributors

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102085.

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