Peer Review File

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Reviewer Comments

Reviewer A

The authors have submitted a very detailed narrative review regarding the field of axillary surgery in breast cancer. They are addressing all known techniques with their pros and caveats and they are combining the presentation of the data with very sound considerations regarding clinical implications. The manuscript is well written (except for some typos). I only have a few comments.

Comment 1:
The authors state that data of the SOUND trial are pending. They have been presented in February 2023 and have recently been published. They should be included and put into context.

Reply 1: I have been reading the publication of the results from the SOUND trial with interest and I am happy to be able to up-date the manuscript with this recent and new information.

Correction in text: Line 151 – 156: "In 2023 the first results on 5-year distant disease-free survival were published from the SOUND trial, including 1405 clinically node negative breast cancer patients with tumor size < 2 cm, randomized to SLND or no axillary surgery. No significant difference was found between groups, indicating that axillary surgery can be safely omitted in breast cancer patients with small, clinically node negative disease. The question that remains to be answered is how to handle the missing information on precise nodal status when planning adjuvant treatment in these patients".
Line 225 - 226: "The decision for adjuvant systemic treatment will be further challenged with the expected results from trials investigating complete omission of axillary staging, like the SOUND trial"
Reference has been added

Comment 2:
In the section on local recurrence the authors sound as if axillary surgery in a clinically node negative axilla in this situation is a standard which it certainly is not. Please elaborate what the benefit of this escalation of surgery is and please add robust references demonstrating that this radical approach is beneficial. Or elaborate that this is an option in selected patients after informed consent about the lacking scientific rationale for this approach. Personally, I would recommend deleting this section.

Reply 2: Previously, ALND was the standard treatment in these patients. This procedure has been abandoned in many centers but still no consensus guidelines exist on handling of the axilla at local recurrence. Axillary staging and treatment in case of

metastases at local recurrence is an area with limited evidence and I therefor chose to keep this part to point out the evidence gap.

Correction in text: Line 319 - 322: “It is possible that the SLND can be repeated in these patients sparing them an ALND for the second time” has been exchanged for “Previously, ALND was recommended in these patients due to uncertainty of the reliability of SLND after prior axillary surgery. Today, no consensus guidelines exist on the optimal axillary staging procedure in case of local recurrence”.

Reviewer B

The author presents a narrative review on axillary surgery in oncologic breast surgery with a focus on current surgical de-escalation. The review is well structured and comprehensively summarizes the current evidence.

Comment 1:

Abstract. Conclusions: Please consider rephrasing the sentence on „The lack of knowledge on precise axillary status will however hamper the possibilities of de-escalating adjuvant systemic treatment and cooperating studies between oncologists and breast surgeons as well as investigations on the use of axillary imaging for staging is needed.“ Consider re-wording to e.g., „ The lack of knowledge on precise axillary status will require smart cooperating studies between oncologists and breast surgeons in order to avoid escalation of systemic treatment due to the lack of applicability of trial eligibility criteria. Furthermore, investigations on the use of axillary imaging for staging are needed.“ Please also consider rephrasing this sentence in the conclusion of the main body.

Reply 1: The suggested rephrasing, has been added to the conclusion in the abstract and main body

Changes in text: Rephrasing of line 30 - 35 and line 378 - 379

Comment 2:

Minor english improvements necessary – use „have shown“ instead of „has shown“ in Background and Objective; „have been included“ instead of „hast been included“ in the Methods.

Reply 2: grammatic corrections have been made

Changes in text: grammatic corrections have been made in line 18, 23, 68 and 74

Comment 3:

Main body. Omission of ALND

Please rephrase the subtitle to „Omission of ALND in the upfront surgery setting“

Reply 3: I agree that it should be mentioned in the subtitle, that this section is regarding primary surgery and not surgery after neoadjuvant treatment.

Correction in text: The subtitle has been extended to: “Omission of ALND at primary surgery”. Likewise, the subtitle “Omission of axillary staging” has been extended to “Omission of axillary staging at primary surgery”

Comment 4:
First and second paragraph: please state in one of the opening sentences and reinforce that these studies included clinically node-negative patients.

Reply 4: I agree that it should be more clear that this concerns clinically node negative breast cancer

Correction in text: the words “clinically node negative breast cancer patients” has been added in line 96 and 111

Comment 5:
Lines 136-137: please rephrase to „ALND is still recommended in breast cancer patients diagnosed as node-positive with preoperative histologic confirmation. This group of patients is being considered to have larger metastatic burden in the axilla.“

Reply 5: Correction has been made as suggested

Correction in text: Line 131 and 134

Comment 6:
Lines 143-145: please rephrase to „The randomized TAXIS trial is currently investigating whether ALND can be replaced by axillary radiotherapy in patients with histologically confirmed node-positive disease undergoing upfront surgery.“

Reply 6: Correction has been made as suggested, apart from the line “undergoing upfront surgery”, as the TAXIS trial includes patients with upfront surgery and surgery after NACT

Correction in text: Line 138

Comment 7:
Line 223: please remove „on axillary ultrasound“.

Reply 7: Correction has been made as suggested

Correction in text: Line 215

Comment 8:
Lines 295-313: please consider mentioning the OPBC-05/EUBREAST-14/ICARO study investigating the nodal recurrence in patients with ITCs after NACT in an international multicenter retrospective cohort analysis with primary results expected at SABCS 2023.

Reply 8: This interesting study on de-escalation of axillary surgery after NACT has been included in the section on axillary staging after NACT

Correction in text: The inclusion of a fourth study on de-escalation on axillary surgery after NACT has resulted in changes from line 291 - 301: “Due to an expected high risk of residual, chemotherapy-resistant metastatic burden in the axilla after NACT, ALND is recommended in most centers in case of residual metastases found at axillary staging after NACT. The risk of axillary recurrence after NACT, if ALND is omitted despite metastases found at staging, is currently being investigated in several studies. In the prospective Italian NEONOD 2 study, ALND is performed for macrometastases in the sentinel node, but no further treatment in case of ITC or micrometastases. The primary endpoint is disease free survival. The retrospective OPBC-05/EUBREAST-14R/ICARO study, includes patients with residual ITC after NACT treated with either ALND, axillary radiotherapy or observation and is investigating 3-year axillary recurrence rate. In the American ALLIANCE A011 202 study (ClinicalTrials.gov identifier: NCT01901094), patients with limited residual metastases in the sentinel node after NACT are randomized for ALND or axillary radiotherapy in case of limited residual metastases in the sentinel node after NACT to compare recurrence free survival”.

Comment 9:
Line 309: please correct TAD to „TAS – tailored axillary surgery“ which is the correct term of the surgical procedure in the TAXIS trial.

Reply 9: This has been corrected

Correction in text: “TAD” replaced by “targeted axillary surgery”, line 305

Comment 10:
Minor english improvements necessary – please reword „Tracer Teknik“ to „Tracer Technique“; Line 195 please correct to „life-long“

Reply 10: Grammar and typo corrections have been made

Correction in text: line 18, 23, 68 and 74

Reviewer C

Comment 1:
In my opinion, this paper presents a somewhat limited vision on certain issues that already carry a quite broad consensus among the breast surgeons community. For instance, RH+/HER2- patients con with one o two positive axillary nodes at diagnosis, who are not to receive neoadjuvant chemotherapy, may avoid an ALND if just these one or two are positive nodes and the SLND retrieved are negative.

Reply 1: This comment is perceived to concern patients with luminal subtypes and 1 – 2 positive lymph nodes. These patients could be spared an ALND if offered primary surgery whereas ALND is offered after NACT in case of non-axillary pCR. Axillary pCR is only seen in 15 – 20% of these patients and it is very likely that the patient will not benefit from less surgery after NACT, compared to primary surgery where they could be spared an ALND. I agree that this is an important issue that ought to have some attention in the review.

Correction in text: Line 309 – 314: "The axillary response to NACT vary between subtypes and only around 15 – 20% of node positive patients with luminal subtypes will achieve an axillary pCR. This means that patients with luminal subtypes and 1 – 2 positive lymph nodes, who could be spared an ALND if offered primary surgery, would most likely be offered an ALND after NACT. As long as ALND is recommended for all patients with residual axillary metastases after NACT, these patients will get more and not less axillary surgery after NACT. This should be taken into consideration when planning treatment"
Reference has been added on axillary pCR