Peer Review File

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Reviewer A

This narrative review gives the reader with an up-to-date knowledge of the current literature and provides the arguments why the breast reconstructive patient should be given this opportunity.

The paper systematically describes the findings and the subparagraphs and corresponding headings are used properly and continuously throughout the paper.

Please find below my few comments and remarks:

ABSTRACT
The abstract somewhat covers the content of this narrative review but a few aspects are missing. It lacks a definition of timing of reconstruction (see below). In addition, the structure of the paper (first describing normal anatomy and hence the side-effect of breast cancer surgery, followed by the technical aspects should be added to the abstract, to fully justify reading the paper. The abstract should also mention the thorough description of the abdominal donor site as well as alternative donor-sites.
Reply: Thank you for the comment and advice. We have added the mentioned aspects to the abstract, hopefully better justifying reading the paper. (page 2, lines 35-45)

INTRODUCTION
The introduction is well written but misses a definition on the timing of autologous reconstruction (immediate or delayed). Does the review cover both (innervation of the native skin envelope and re-innervation of the flap) or just delayed reconstruction (re-innervation of the flap)? This should be clearly presented in the introduction.
Reply: Thank you for the comment. We have now specifically mentioned immediate and delayed reconstruction in the introduction, to emphasize that both timings are included. The reinnervation of autologous breast reconstruction utilized by most reconstructive surgeons, both in immediate as well as delayed reconstruction, is always related to attaching a sensory nerve from the donor site (the flap) to a sensory nerve at the recipient site. As we know from previous studies, this also influences sensory return in the native skin envelope, but the native skin envelope itself is not directly reinnervated. Direct reinnervation of the native skin is described in the current literature, for example in the case of targeted nipple areola complex reinnervation, but the number of publications is sparse. (page 5 line 86)

METHODS
This paragraph is sufficient. Please state why only PubMed and not also EMBASE, was used for the literature search. Please add to Table 1 by initials who of the authors screened the papers.
Reply: Thank you for the comment. We have only reviewed PubMed and references of the included articles, as this likely contains the majority of relevant publications. Publications on sensation of the breast are still upcoming and the relatively small

number of publications in relation to other major topics decreases the chance of missing important publications in other databases. We have now added an explanation to the text. We have also added initials to the authors who screened the papers to Table 1. (page 5 lines 102-103)

RESULTS
The results section is rather long (lines 92-433), but systematically and concisely describes the anatomy, outcomes at the breast/thoracic region and at the different donor-sites.

Please find below, my comments (if any) to each of the paragraphs:

Sensation in the normal breast and donor site (lines 102-212)

This paragraph is well written and presents the current knowledge elegantly to the reader.
Reply: Thank you for the compliment.

Line 102 – should be donor sites.
Reply: Thank you. We have changed the word *site* to *sites*. (page 7 line 119)

Lines 203-208- this subparagraph should be placed and further perspectivized in the discussion/conclusion.
Reply: Thank you for the comment. The importance of patient-reported outcome measures more focused on breast sensation is highlighted in several parts of the results (page 10-11 lines 206-210, page 13-14 lines 277-281, page 23 lines 455-459), and in the second paragraph of the discussion (page 23-24 lines 473-477). Besides this, we have added this to emphasize its importance in the conclusion (page 27 lines 556-558).

Sensation in the operated breast (lines 214-255)

Line 217 – please distinguish between radical mastectomy, skin-sparing mastectomy, and nipple-sparing mastectomy.
Reply: Thank you for the comment. There was already a small note on nipple-sparing mastectomy, but we have now specifically added that and which type of mastectomy influences sparing of the sensory nerves. (page 11 lines 216 and 222)

Lines 231-232 – please specify if the preserved nerves could be coapted during immediate breast reconstruction and/or delayed breast reconstruction (BR).
Reply: Thank you for the comment. As mentioned in one of our earlier comments, nerve coaptation can be combined with immediate as well as delayed breast reconstruction. The reference by Peled et al. refers to an immediate implant-based breast reconstruction. However, other forms of reconstructions more commonly accompanied by nerve coaptation can also be used, such as autologous breast reconstruction with a free flap. This method has not been described in delayed reconstructions. This was further specified in the manuscript. (page 11 lines 224,225,230,231)

Lines 235-240 – please also here specify if this is the case for immediate and/or delayed BR.
Reply: Thank you for the comment. We have specified this further in the text. As also hypothesized by Bijkerk et al., in delayed reconstructions, the skin has to be stretched out further compared to immediate implant-based reconstructions. Hence, breast sensation is impaired in both reconstructions but may be repaired more in delayed compared to immediate breast reconstructions. (page 11 lines 224,225,230,231)

Lines 248-249 – please comment on the importance of informing patients on "numbness".
Reply: Thank you for the comment. We have added a more elaborate paragraph on the importance of informing patients on the numbness to the text. (page 12-13 lines 256-281)

Restoring sensation (lines 257-433)

Lines 259-292 – this paragraph is very good and informative, leaving the reader with the relevant insight. Please add a sentence on why the systematics of the paper is deviated from in the present paragraph.
Reply: Thank you for the comment. Initially we used this order in the text, as during surgery the surgeon will usually begin with flap dissection at the donor site, followed by reconstruction of the breast itself. However, in the light of a logical order in the text and not making much difference to the flow of the text, we have interchanged the two paragraphs to adhere more to the systematics of the paper. (page 14-15)

Lines 343-355 - please again clarify if these findings are in immediate or delayed BRs. The reader should be able to understand this without reading the relevant reference (76).
Reply: Thank you for the comment. As mentioned in the text, nerve coaptation improves sensory recovery of the breast, regardless of reconstructive timing. We have further specified this based on the results of Beugels et al. (page 18, lines 352-356)

Lines 357-378 – this paragraph is well written and leaves the reader with a comprehensive overview of the literature.
Reply: Thank you for the compliment.

Lines 392-433

Line 433 – this sentence could be elaborated on in the discussion.
Reply: Thank you for the comment. We have elaborated more on the donor site sensation and related patient-reported outcome measures in the discussion. (page 24 lines 478-485).

DISCUSSION AND CONCLUSION
Lines 465-467 – could encompass comments on including for instance neurologists with a special interest in pain/sensation, thus performing the studies with participation of specialized scientific collaborators.

Reply: Thank you for the comment. For the randomized controlled trial we are currently conducting, investigating the effect of a nerve coaptation on quality of life and sensation recovery of the DIEP flap, we have discussed this matter with specialists in the field and are therefore measuring more modalities of sensation than has currently be done; measuring static touch, moving touch, and temperature. Hopefully in this way, we will set an example for future research projects on breast sensation.

Lines 483-488 – beautiful perspective!
Reply: Thank you for the compliment.

Lines 489-496 – Fully agree and add a perspective on inclusion of for instance neurologist as above.
Reply: Thank you for the comment. We have added the suggestions regarding multidisciplinary collaborators to the text. (page 26, lines 539-541).

The conclusions drawn are fully justified.
Reply: Thank you for the compliment.

REFERENCES
The references comprise the entity of the current literature.
Reply: Thank you for the confirmation and compliment.

FIGURES
The figures are in fact works of art and diligently underlines the anatomical and surgical aspects of paper.
Reply: Good to hear that the figures are clear and well-composed. Thank you for the compliment.

Reviewer B

- The authors are congratulated on a well-rounded and thoroughly in-depth narrative review of the literature on sensory recovery and innervated flaps. The information is well presented and discussed throughout the paper and provides a valuable resource for readership.
Reply: Thank you for the compliment. We are delighted to hear that the paper is valuable to other colleagues.

- Minor corrections would include grammar in the abstract and manuscript to correct incomplete sentences, etc.
Reply: This is now checked and improved by two separate authors.

- The reference to the narrative review checklist can be removed from the manuscript, though the use of this checklist is appreciated.
Reply: Thank you for the comment. We have removed the reference and sentence from the manuscript.

Reviewer C

The paper is a valuable capture of clinical evidence that has the potential to inform clinicians about best practice, improving functional, aesthetic and patient-experiential ways. The narrative review checklist was used and there is some level of rigour in the method.

There are a number of broad issues that the paper needs to address for a number of its claims to be convincing. Given the nature of these the Recommendation of 'Major Revision' has been made. These revisions entail review of the entire paper to ensure the review has more explicit argumentation and is congruent with the ethos of patient focused care and thus the implications drawn out of the review.

Revisions:

The authors allude to the quality of the research included but there is no infucation that a quality assessment tool was used to evaluate (and thus with confidence and clarity) the literature.

Reply**:** Risk of bias and/or level of evidence of the included studies was not specified as this is not common practice in a narrative review. However, we based these statements on the systematic reviews that we included in our reference list (10-14, 47) that did perform quality assessment. This is now added to the discussion. (page 25, line 504-508)

On multie ocassions the authirs claim that "loss of sensation is unpleasant and unanticipated". However, at no point do the authors consider the implications of this for patient care. The most obvious recommendation would be for clinicians to explain this to patients as part of routine care. Now, this undoubtably occurs in some cases, but the opportunity to link this to the authors reference to the changed landscape of patient care (eg. PROMs) is missed.

Reply: Thank you for this helpful insight, we added paragraphs emphasizing the link with and importance of patient education and PROM outcomes. (page 12-13, lines 256-281)

Related to the previous point, more space could be given to implications for practice, and perhaps trimming the first section of the results which is more routine description or reportage than critical synthesis. The authors refer to this section as a description of fundamental and clinical knowledge (Ln.94). But, the content would benefit from a more clearly critical handling, or some editing for key headlines (essential for usefulness) to be drawn out.

Reply: Thank you for this suggestion. We agree that the clinical implications deserve to be highlighted more. Therefore, we added a subheading ‘Clinical implications’ to each of the three sections of the manuscript. The other subheadings were shortened wherever possible, accordingly. (page 10-11 lines 199-210, page 13 lines 263-281, page 22-23 lines 439-459).

Across the review the authors use 'qualitative outcomes' to refer to measures that are technically quantitative (eg. patient ordinal self-ratings using Likert scales). Perhaps a more appropriate phrasing would be 'quality of patient experiences' - less concise but more accurate, technically.

Reply: Thank you for this well-noticed suboptimal choice of terminology on our side, and your suggestion to improve it. We changed the phrase ‘qualitative outcomes’ to ‘patient-reported outcomes’ as we felt this is still more accurate and in line with other research, making it immediately familiar and understandable for the readers.

Related to the previous point, the authors are advised to check the review to ensure terms such as 'satisfaction' and 'quality of life' are not used superficially to describe any outcome measure that is not 'clinical'.

Reply: We checked each mention of both terms, and concluded that we only used either term if the referenced publication assessed this using a PRO tool (in nearly all cases this was the BREAST-Q). We therefore believe our use of these terms is in fact justified.

Ln. 396 should be 'gold' not 'golden' standard?

Reply: Indeed, we corrected this. Thank you for noticing.